ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS IN THE SETTING OF CHRONIC KIDNEY DISEASE

by
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Abstract

Angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are the mainstays of therapy for hypertension, heart failure with reduced ejection fraction, and coronary artery disease. Additionally, multiple clinical guidelines recommend an ACE-I or ARB to be used in chronic kidney disease (CKD) patients with elevated albuminuria. However, how albuminuria measures relate to the prescription of ACE-I/ARB is unclear. Despite the benefits of ACE-Is and ARBs, they may predispose to hyperkalemia and acute kidney injury, risks that are particularly high among patients with low estimated glomerular filtration rate (eGFR). Clinical evidence is lacking regarding the risk-benefit balance of discontinuing ACE-I/ARB in patients with advanced CKD.

Using electronic heath records data from the Geisinger Health System, we assessed the utilization pattern of ACE-Is and ARBs in real-world clinical practice, and applied causal inference tools to investigate the associations of ACE-I/ARB discontinuation with health outcomes.

In a cohort of individuals without recorded contraindications or allergy to ACE-I/ARB, only 43.1% of individuals with albumin-to-creatinine ratio (ACR) > 300 mg/g and 40.9% of those with diabetes and ACR >30 mg/g initiated ACE-I/ARB within 6 months of the ACR measurement. We also found that individuals with higher levels of albuminuria were more likely to initiate ACE-I/ARB, providing evidence that results from albuminuria testing change patient care. Among users of ACE-I/ARB, we estimated that the majority had a therapy discontinuation by 5 years after therapy initiation. There were strong associations of advanced CKD stages with therapy discontinuation, with patients with G4 CKD (eGFR: 15-29 ml/min/1.73 m^2) more than twice as likely to discontinue therapy compared to people with eGFR ≥90 mL/min/1.73m^2.

Among users with an eGFR decline to below 30 ml/min/1.73 m^2, ACE-I/ARB discontinuation after the eGFR decline was associated with higher risks of mortality and major adverse cardiovascular events, and no significant difference in the risk of end-stage kidney disease.

In conclusion, continuing ACE-I/ARB in patients with declining renal function may provide cardiovascular and survival benefits. However, ACE-I/ARB discontinuation is common especially among users with advanced CKD stages. Our findings suggest that adherence to albuminuria testing provides an opportunity to enhance utilization of ACE-I/ARB.

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Chapter 1. Introduction

Background

Angiotensin Converting Enzyme Inhibitors (ACE-Is) and Angiotensin Receptor Blockers (ARBs) are widely prescribed medications indicated for a number of chronic conditions. They are the mainstays of therapy for hypertension, heart failure with reduced ejection fraction, and coronary artery disease.[1–6] Additionally, multiple clinical guidelines recommend the use of an ACE-I or ARB in patients with elevated albuminuria,[4,7,8] as these medications provide cardio- and kidney-protective effects, particularly in the presence of albuminuria.[1–7,9] For example, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest use of an ACE-I or ARB as an antihypertensive agent "in diabetic adults with chronic kidney disease (CKD) and urine albumin excretion 30–300 mg/24 hours" and "in both diabetic and non-diabetic adults with CKD and urine albumin excretion > 300 mg/24 hours".[7] In part due to these recommendations, testing for albuminuria is suggested for people at higher risk of CKD including those with hypertension, diabetes, or 65 years of age or older.[10,11] However, how the results of albuminuria testing relate to the prescription of ACE-I/ARB therapy is uncertain.

Despite the benefits of ACE-Is and ARBs, they may cause acute reduction in glomerular filtration rate (GFR) following their initiation, and also increase the risk of hyperkalemia and acute kidney injury.[12–14] Ultimately, treatment decisions are made based on the perceived balance between the benefits and the risks. In the setting of CKD progression, the risk-benefit balance may vary as GFR declines. While side effects of ACE-I/ARB can affect patients across all CKD stages, some side effects are more

concerning in patients with advanced CKD stages. For example, acute reduction in GFR can cause more harm for patients with lower GFR. In addition, patients with lower GFR are at increased risk of hyperkalemia and acute kidney injury, which can be compounded by the use of ACE-Is and ARBs as a result of the potential side-effects. However, the renal-protective effect and other benefits may still remain for patients with lower GFR. Currently, it is unclear whether risks may start to outweigh benefits as CKD progresses to advanced stages, and therefore there remain to be controversies regarding whether ACE-Is and ARBs should be discontinued in advanced CKD patients.

Clinical evidence is lacking regarding the efficacy and safety of ACE-I and ARB in patients with advanced CKD. This is partly attributable to the fact that patients with advanced CKD are generally underrepresented in clinical trials.[15] Additionally, most clinical trial studies are focused on evaluating the efficacy of initiating a therapy; in contrast, the impact of treatment discontinuation has been relatively understudied. As a result, there is equipoise regarding the risk-benefit balance of discontinuing ACE-I/ARB in patients with advanced CKD.[14,16]

Clinical guidelines reflect this uncertainty and remain vague as to whether ACE-I/ARB needs to be discontinued in patients with advanced CKD, leaving patients and providers to navigate these questions without clear guidance. For example, the Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends "temporary discontinuation" of ACE-I/ARB "in people with a GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI"; yet also states "do not routinely discontinue [ACE-I/ARB therapy] in people with GFR

<30 ml/min/1.73 m^2 as they remain nephroprotective".[7] Currently, discontinuation of ACE-I/ARB relies largely on expert opinion in clinical practice.

Little has been done to assess the pattern of discontinuing ACE-I/ARB across the spectrum of kidney function in real-world clinical practice. Existing data on the rates of ACE-I/ARB discontinuation largely originated from clinical trials.[17] A meta-analysis of 22,542 patients without heart failure across eight randomized controlled trials showed a pooled discontinuation rate of 6.5% and 4.9% for ACE-I and ARB users, respectively, over an average of 3.4 years of follow-up.[18] However, drug utilization patterns in clinical trials are unlikely to reflect those in real-world practice.

Objectives

The overarching goal of this dissertation was to fill the knowledge gap with regards to ACE-I/ARB use in the context of CKD. We used electronic health records data from a community-based cohort receiving primary care in the Geisinger Health System. Specifically, we investigated the following research questions.

1) We evaluated the association of albuminuria levels with the prescription of ACE-I and ARB in real-world clinical practice, given established benefits of ACE-I/ARB in patients with elevated albuminuria. We hypothesized that higher levels of ACR would be associated with greater utilization of ACE-I/ARB, supporting the notion that adherence to albuminuria testing guidelines can change management.
2) Given the uncertainty regarding whether and when ACE-I/ARB should be discontinued in the setting of CKD, we assessed the real-world practice patterns of discontinuing ACE-I/ARB across CKD stages and identified factors independently associated with ACE-I/ARB discontinuation. We hypothesized that patients with

more advanced CKD stage at the time of ACE-I/ARB initiation would be more likely to discontinue therapy earlier; hyperkalemia, AKI-related hospitalization, hypotension, and low bicarbonate level would be associated with higher risk of ACE-I/ARB discontinuation; concurrent use of potassium-lowering agents, such as thiazide and loop diuretics, would be associated with lower risk of ACE-I/ARB discontinuation.

3) We investigated the association of ACE-I/ARB discontinuation after eGFR declines to below 30 ml/min/1.73m^2 with the risk of mortality, major adverse cardiovascular events (MACE), and end-stage kidney disease (ESKD). We hypothesized that ACE-I/ARB discontinuation would be associated with higher risk of mortality, MACE, and ESKD.

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Chapter 2. Association of Albuminuria Levels with the Prescription of Renin-Angiotensin System Blockade

Abstract

Multiple clinical guidelines recommend an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) in patients with elevated albuminuria, which can be measured through urine albumin-to-creatinine ratio (ACR), protein-to-creatinine ratio (PCR), or dipstick. However, how albuminuria test results relate to the prescription of ACE-I/ARB is uncertain. We identified individuals with an ACR measurement between January 1, 2004 and June 30, 2018, and no contraindications or allergy to ACE-I/ARB. We performed multivariable logistic regression analyses to

evaluate the association between ACR level and prescription of ACE-I/ARB within six months after the test. We applied similar methods to investigate the association of PCR and dipstick measurement results with the prescription of ACE-I/ARB. Among 67,237 individuals with an ACR measurement, 47.7% were already taking an ACE-I or ARB at the time of first ACR measurement. Among the 35,138 individuals who were not on ACE-I/ARB, those with higher ACR levels were more likely to be prescribed ACE-I/ARB in the following 6 months, with steep increases in prescriptions until ACR 300 mg/g, after which the association plateaued. The majority (80.9%) of ACE-I/ARB prescriptions were made by family medicine and internal medicine. A similar pattern held in the cohorts tested by PCR and dipstick measurement. Our study provides evidence that albuminuria test results change patient care, suggesting that adherence to albuminuria testing is a key step in optimal medical management.

Key words: albuminuria, urine albumin-to-creatinine ratio, urine protein-to-creatinine ratio, antihypertensive, angiotensin converting enzyme inhibitors, angiotensin receptor blockers

Introduction

Albuminuria, defined as a urine albumin-to-creatinine ratio (ACR) ≥ 30 mg/g, is a pathologic condition which reflects kidney damage.[1–3] Higher levels of albuminuria are associated with increased risks of adverse kidney events such as end-stage kidney disease, decline in eGFR, and acute kidney injury.[4–6] Additionally, higher levels of albuminuria are associated with greater risks of hypertension, cardiovascular events, and all-cause mortality.[4,5,7–11] Multiple clinical guidelines recommend the use of an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) in patients

with elevated albuminuria,[1,12,13] as these medications provide cardio- and kidney-protective effects, particularly in the presence of albuminuria.[1,12,14–19] For example, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest use of an ACE-I or ARB as an antihypertensive agent "in diabetic adults with chronic kidney disease (CKD) and urine albumin excretion 30–300 mg/24 hours" and "in both diabetic and non-diabetic adults with CKD and urine albumin excretion > 300 mg/24 hours".[1] Similarly, the American Diabetes Association suggests that "in nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) and is strongly recommended for those with urinary albumin-to-creatinine ratio ≥ 300 mg/g creatinine".[20]

In part due to these recommendations, testing for albuminuria is suggested for people at higher risk of CKD including those with hypertension, diabetes, or 65 years of age or older.[21,22] Urine ACR is considered the preferred method of measuring albuminuria, followed by urine protein-to-creatinine ratio (PCR), and urine protein dipstick measurement.[1] Urine ACR between 30 and 300 mg/g and PCR between 150 and 500 mg/g are considered "moderately increased" albuminuria; ACR above 300 mg/g and PCR above 500 mg/g are considered "severely increased" albuminuria.[1] We previously reported that patients who received testing for albuminuria had a lower risk of ACE-I/ARB discontinuation.[23] However, how the results of albuminuria testing relate to the prescription of ACE-I/ARB therapy is uncertain.

Using data from a large, integrated health care system, we identified individuals who received an ACR measurement and studied the association of ACR level with the utilization of ACE-I/ARB. We hypothesized that higher levels of ACR would be associated with higher odds of ACE-I/ARB initiation, supporting the notion that adherence to albuminuria testing guidelines can change management. To discern specific patterns for different albuminuria measurement methods, we also assessed the associations of PCR and dipstick measurement results with the prescription of ACE-I/ARB.

Methods

Study setting and study population

We identified a real-world cohort of individuals who received testing for albuminuria using data from Geisinger, an integrated health system serving 45 counties across central and northeastern Pennsylvania. The electronic health records of the system provide data on patient demographic characteristics, inpatient and outpatient encounters, problem lists, outpatient prescriptions, and laboratory test results.

We identified 83,807 individuals who received an ACR measurement between January 1, 2004 and June 30, 2018. Time of the first ACR measurement was considered the baseline date for each individual. We excluded individuals with any record of allergy to ACE-I/ARB at the time of the ACR measurement (n=3,285). Next, we excluded individuals whose systolic blood pressure was missing or below 100 mmHg based on the latest outpatient measure prior to the time of the ACR measurement (n=4,309), and those with the latest outpatient serum potassium above 5 mEq/L or no serum potassium

measured at or before the time of the ACR measurement (n=6,893). Further exclusion criteria included end-stage kidney disease (n=318), pregnancy within the preceding year (n=1,294), age < 18 years (n=435), and no serum creatinine measurement by the time of the ACR measurement (n=36; **Figure S1**).

Exposure

The primary exposure of interest was ACR, which we log-transformed with a base of 2. To allow for a potentially non-linear relationship, we used linear spline forms of log-transformed ACR with knots corresponding to ACR values at 30 and 300 mg/g.

Outcomes

Prevalent use of ACE-I/ARB was defined as any record of ACE-I/ARB use during the three-month period prior to the ACR measurement. Among individuals who were not prevalent users of ACE-I/ARB, we investigated new prescription of ACE-I/ARB initiation within six months after the ACR measurement.

Baseline covariates

Systolic blood pressure, serum potassium, and serum creatinine at the time of the ACR testing were defined as the most recent antecedent outpatient measure. Glomerular filtration rate (GFR) was estimated using serum creatinine accounting for age, sex, and race based on the CKD Epidemiology Collaboration equation.[24] We used linear spline forms of eGFR with knots at 30 and 60 mL/min/1.73 m^2. We ascertained baseline comorbidities such as diabetes, congestive heart failure, myocardial infarction, and hypertension through the International Classification of Diseases, Ninth Revision,

Clinical Modification (ICD-9-CM) and the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes (**Table S1**). Data regarding statin, thiazide, calcium channel blocker, and beta blocker use at the time of the ACR testing were obtained from medication records. We also obtained demographic characteristics such as age, sex, and race/ethnicity. Calendar year at the time of the ACR testing was categorized into 2004-2008, 2009-2013, and 2014-2018.

Statistical analyses

Baseline characteristics of the study population were described using median (interquartile range) for ACR, mean (standard deviation [SD]) for other continuous variables, and count (percentage) for categorical variables. We performed multivariable logistic regression to assess the association of ACR level and other covariates with the prevalent use of ACE-I/ARB at the time of the ACR measurement.

Among individuals not on ACE-I/ARB at the time of the ACR test, we used kernel density curves to depict the distribution of log-transformed ACR levels stratified by ACE-I/ARB initiation status. We then performed multivariable logistic regression analyses to evaluate the association between ACR level and ACE-I/ARB initiation within six months of the ACR test, adjusting for baseline age, sex, race/ethnicity, calendar year of the ACR test, systolic blood pressure, serum potassium, eGFR, diabetes, congestive heart failure, myocardial infarction, hypertension, use of statin, thiazide, calcium channel blocker, and beta blocker.

Finally, among individuals who initiated ACE-I/ARB within 6 months of the ACR measurement, we assessed the proportion prescribed by providers of different specialties.

Additional analyses

We investigated associations of PCR and dipstick test result with ACE-I/ARB prescription. We applied similar inclusion criteria as described above and identified a cohort of 20,104 adults who received their first PCR measurement between January 1, 2004 and June 30, 2018, and 141,914 adults who received their first dipstick measurement during the same period. PCR was also log-transformed with a base of 2 and it was modeled using spline terms with a knot corresponding to PCR at 500 mg/g given the shape of the association as well as the clinical use of this threshold. Dipstick measurement result was treated as a categorical variable with "++ or above", "+", and "trace or negative" as the reference category. A similar analytic procedure was performed for each of these cohorts.

For all analyses, statistical significance was evaluated at a significance level of 0.05 based on two-sided testing. SAS software, version 9.4 (SAS Institute Inc), Stata, version 15.1 (StataCorp LLC), and R, version 3.6.0 (R Foundation for Statistical Computing) were used for statistical analyses.

This study was approved by institutional review boards at the Johns Hopkins Bloomberg School of Public Health and Geisinger Medical Center. All data were deidentified, and consent was waived.

Results

Study population

There were a total of 67,237 individuals who had an ACR measurement and met the inclusion criteria (**Table 2-1**). Mean (SD) age of the cohort was 60.5 (14.9) years and 33,696 (50.1%) were female. The majority of the cohort had a clinical diagnosis of diabetes (n=36,722, 54.6%) or hypertension (n=49,530, 73.7%). Mean (SD) eGFR was 81 (24.1) mL/min/1.73 m^2, and 14,189 (21.1%) individuals had an eGFR below 60 mL/min/1.73 m^2 at the time of the ACR test. Median (interquartile range) ACR was 9 (4-26) mg/g. ACR ranged between 30 and 300 mg/g for 12,522 (18.6%) individuals and was above 300 mg/g for 2,927 (4.4%) individuals.

Association between ACR level and prevalent use of ACE-I/ARB

A total of 32,099 (47.7%) individuals were on ACE-I/ARB therapy at the time of the initial ACR test. Individuals who were taking ACE-I/ARB therapy were more likely to have higher ACR (odds ratio (OR) per two-fold higher level: 1.11 [95% confidence interval (CI): 1.10-1.12]), serum potassium (OR per mEq/L higher level: 1.45 [95% CI: 1.38-1.52]), systolic blood pressure (OR per 10-mmHg higher level: 1.13 [95% CI: 1.12-1.14]), and eGFR (OR per 5 mL/min/1.73 m^2 higher level: 1.90 [95% CI: 1.70-2.12] for eGFR below 30 mL/min/1.73 m^2; 1.02 [95% CI: 1.01-1.04] for eGFR between 30 and 60 mL/min/1.73 m^2; and 1.01 [95% CI: 1.00-1.02] for eGFR above 60 mL/min/1.73 m^2). Additionally, ACE-I/ARB use at the time of the test was positively associated with the presence of diabetes (OR: 1.17 [95% CI: 1.13-1.21]), congestive heart failure (OR: 1.11 [95% CI: 1.04-1.19]), hypertension (OR: 3.77 [95% CI: 3.59-3.95]), statin use (OR: 1.46

[95% CI: 1.41-1.51]), thiazide use (OR: 1.61 [95% CI: 1.55-1.67]), and black race (OR: 1.23 [95% CI: 1.12-1.34]), and negatively associated with beta blocker use (OR: 0.83 [95% CI: 0.80-0.86]), older age (OR per 10-year higher age: 0.94 [95% CI: 0.92-0.95]), female sex (OR: 0.94 [95% CI: 0.91-0.98]), and more recent years (OR: 0.88 [95% CI: 0.84-0.92] and 0.86 [95% CI: 0.82-0.89] for year 2009-2013 and 2014-2018, respectively, compared with year 2004-2008).

Association between ACR level and initiation of ACE-I/ARB

Among the 35,138 individuals who were not on ACE-I/ARB at the time of the test, 6,514 (18.5%) initiated ACE-I/ARB within 6 months. The proportion who initiated an ACE-I/ARB was 13.6%, 35.6%, and 43.1% among individuals with ACR <30, 30-300, and >300 mg/g, respectively. Among the 4,621 individuals with diabetes and ACR above 30 mg/g, 1,889 (40.9%) initiated ACE-I/ARB. Among the 426 individuals with ACR above 300 mg/g and no diabetes, 162 (38.0%) initiated ACE-I/ARB. Those who initiated ACE-I/ARB had a distribution of ACR more skewed toward higher levels than those who did not (**Figure 2-1**). Multivariable logistic regression showed significantly higher odds of initiating ACE-I/ARB with higher levels of ACR for ACR below 30 mg/g (OR per two-fold higher ACR: 1.33 [95% CI: 1.30-1.37]) and between 30 and 300 mg/g (OR: 1.34 [95% CI: 1.29-1.40]), but no significant difference associated with further increase in ACR above 300 mg/g (OR: 1.01 [95% CI: 0.93-1.10]; **Figure 2-2**). Additionally, ACE-I/ARB initiation within six months of the ACR measurement was positively associated with higher serum potassium, systolic blood pressure, eGFR, statin use, thiazide use, black race, the presence of diabetes, and hypertension, and was negatively associated with beta

blocker use, calcium channel blocker use, previous diagnosis of congestive heart failure, older age, female sex, and more recent years (**Table 2-2**). Among those who initiated ACE-I/ARB, 80.9% were prescribed by family medicine and internal medicine, 1.8% by endocrinologists, 1.5% by cardiologists, 1.4% by nephrologists, 1.0% by emergency medicine, and the remaining 13.4% by providers of other specialties.

Results in cohorts with PCR and dipstick measurement

A total of 20,104 individuals with a PCR measurement and 141,914 individuals with a dipstick measurement met the inclusion criteria (**Table 2-S 2, 2-S 3**). Compared with the cohort tested with ACR, prevalence of diabetes was lower in the PCR and dipstick cohorts (33.4% and 15.3% vs. 54.6%). In contrast, the proportion with eGFR below 60 mL/min/1.73 m^2 was the highest among those tested by PCR (57.2%), followed by ACR (21.1%), and dipstick (12.6%). The majority had hypertension among those tested by PCR (79.3%) and ACR (73.7%), but less than half had hypertension by the time of the initial dipstick measurement (46.9%).

Among the 20,104 individuals who had a PCR measurement, median (interquartile range) PCR was 110 (68-260) mg/g, and 10437 (51.9%) individuals were on ACE-I/ARB therapy at the time of the initial PCR test. Individuals who were taking ACE-I/ARB therapy were more likely to have higher PCR only for those with PCR above 500 mg/g (OR per two-fold higher PCR: 1.07 [95% CI: 1.02-1.12]), adjusting for baseline covariates. Interestingly, there was an inverse association between higher levels of PCR and prevalent use of ACE-I/ARB for PCR below 500 mg/g (OR per two-fold higher PCR: 0.94 [95% CI: 0.91-0.97]).

Of the 9,667 individuals who were not on ACE-I/ARB at the time of the PCR test, 912 (9.4%) initiated ACE-I/ARB within 6 months. Individuals who initiated ACE-I/ARB within 6 months of the PCR test had a distribution of PCR levels that was more skewed toward the higher range, compared with those did not initiate ACE-I/ARB (**Figure 2-S 2**). Higher PCR was independently associated with a significantly higher odds of ACE-I/ARB initiation (OR per two-fold increase in PCR: 1.47 [95% CI: 1.36-1.58] for PCR below 500 mg/g and 1.35 [95% CI: 1.23-1.48] for PCR above 500 mg/g; **Figure 2-S 3**). Among those who initiated ACE-I/ARB, 45.8% were prescribed by family medicine and internal medicine, 29.6% by nephrologists, 2.4% by cardiologists, 1.9% by emergency medicine, 0.9% by endocrinologists, and the remaining 19.4% by providers of other specialties.

Among the 141,914 patients who received a dipstick measurement, 39,664 (27.9%) individuals were on ACE-I/ARB therapy at the time of the initial dipstick measurement. Compared with a negative dipstick test result, having a result of "+"was negatively associated with prevalent ACE-I/ARB use (OR: 0.95 [95% CI: 0.91-0.99]); whereas a result of "++ or above" was not associated with a significant difference in prevalent ACE-I/ARB use (OR: 1.09 [95% CI: 0.99-1.21]).

Among the 102,250 individuals who were not on ACE-I/ARB at the time of the dipstick measurement, 5,234 (5.1%) initiated ACE-I/ARB within 6 months. Compared with a negative test result, both results of "+" (OR: 1.25 [95% CI: 1.16-1.36]) and "++ or above" (OR: 1.54 [95% CI: 1.29-1.84]) were independently associated with a higher odds of ACE-I/ARB initiation within 6 months of the test. Among those who initiated ACE-

I/ARB, 78.5% were prescribed by family medicine and internal medicine, 3.4% by cardiologists, 2.9% by nephrologists, 1.0% by emergency medicine, 0.6% by endocrinologists, and the remaining 13.6% by providers of other specialties.

Discussion

Our study investigated the utilization of ACE-I/ARB in a large, real-world patient cohort who were tested for albuminuria. Almost half were already on ACE-I/ARB at the time of the initial ACR test. Those on ACE-I/ARB at the time of the test were more likely to have hypertension, diabetes, and congestive heart failure, which is not surprising given established benefits of ACE-I/ARB for these conditions.[1,12,14,15,17] Interestingly, older individuals were less likely to be on ACE-I/ARB at the time of the test. This finding was consistent with previous studies that observed underutilization of ACE-I/ARB among older adults.[25,26] Among individuals not already taking ACE-I/ARB at the time of the albuminuria test, higher ACR was positively associated with initiating ACE-I/ARB in the subsequent six months. Interestingly, the association plateaued for ACR levels above 300 mg/g; in other words, although an individual with ACR 1000 mg/g was much more likely to be prescribed an ACE-I/ARB than someone whose test showed ACR 29 mg/g, the individual was not more likely to be prescribed an ACE-I/ARB than someone with ACR 300 mg/g. In comparison, higher PCR was positively associated with ACE-I/ARB initiation for PCR levels both above and below 500 mg/g. This observation may reflect the fact that ACR above 300 mg/g is an unambiguous indication for prescribing ACE-I/ARB, with no difference in guidance with respect to ACE-I/ARB prescription once ACR passes the threshold of 300 mg/g. In comparison, the conversion of PCR to ACR is approximate, with less clear guidance on when to initiate an ACE-I/ARB, which may

explain a positive association between PCR levels and ACE-I/ARB initiation across the whole range of PCR. Alternatively, it may reflect the specialty of the provider who managed the patients. Nephrologists may be more likely to both order PCR measurement to test for albuminuria and to prescribe ACE-I/ARB therapy. For example, among individuals who were prescribed ACE-I/ARB following a PCR measurement, 29.6% received prescriptions from nephrologists, compared with 1.4% among those who initiated ACE-I/ARB following an ACR measurement. Similarly, cardiologists' prescription of ACE-I/ARB therapy was higher in patients with PCR measured compared to ACR.

This study suggests that some providers follow clinical guidelines recommending ACE-I/ARB use in individuals with elevated albuminuria, however, many others do not. For example, in this cohort of individuals without recorded contraindications to ACE-I/ARB such as hyperkalemia, hypotension, or allergy to ACE-I/ARB, only 43.1% of those with ACR > 300 mg/g and only 40.9% of individuals with diabetes and ACR >30 mg/g initiated ACE-I/ARB within 6 months of the test. Underutilization of ACE-I/ARB was also observed in a previous study reporting that 54% of the diabetic patients with albuminuria received ACE-I/ARB.[27] Of note, these utilization rates were obtained among individuals who were tested for albuminuria. Underutilization would likely be higher among individuals who do not undergo albuminuria testing.

While individuals with previous diagnosis of congestive heart failure were more likely to be on ACE-I/ARB at the time of the ACR measurement, those who were not on ACE-I/ARB at the time of the ACR measurement were less likely to initiate ACE-I/ARB

after the ACR measurement. This may reflect selection bias: those who were not on ACE-I/ARB already may have intolerance or a contraindication to therapy. However, previous studies suggest underutilization of ACE-I/ARB among individuals with congestive heart failure may be due to fear of adverse events such as kidney function deterioration and hypotension, and insufficient appreciation of the benefits of these medications or the prognostic implications of heart failure.[28–30] Our findings similarly highlight underutilization of ACE-I/ARB among individuals with elevated albuminuria. Given that the majority of the population received prescriptions from family medicine and internal medicine providers, educational efforts focused on these providers may help overcome barriers of ACE-I/ARB utilization among individuals with elevated albuminuria.

There are several limitations of this study. First, we used medication prescription records to ascertain ACE-I/ARB use. Therefore, our study results reflect the pattern in ACE-I/ARB prescription rather than the actual dispensing or use of these medications. Second, data were not captured for drug classes such as sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide 1 receptor agonists, since randomized controlled trials supporting their indications in individuals with albuminuria were first published near the end of the study period. Third, the study cohort was mainly white and our findings may thus have limited generalizability to other racial and ethnicity groups. Fourth, albuminuria level was based on only one measurement. Fifth, we did not take dosage into consideration. Future studies are needed to evaluate dosage of ACE-I/ARB in real-world clinical practice to examine potential opportunities to maximize therapeutic potential. Sixth, our study was from a primarily rural setting, which may have limited access to

specialty care. Therefore, the observed ACE-I/ARB utilization patterns may not generalize to urban settings. Finally, we were unable to account for socioeconomic status.

Our study assessed the association between albuminuria test results and the prescription of ACE-I/ARB in a large, integrated health system. We examined the pattern for patients with ACR, PCR, and dipstick measurement individually. Instead of categorizing ACR and PCR values into "normal to mildly increased", "moderately increased" and "severely increased" albuminuria, we evaluated a continuous form of these variables with splines in the model to provide insights on the effect of increase in the measurement within each category while comprehensively addressing indications and contraindications for the initiation of ACE-I/ARB. Finally, we excluded people with recorded allergies to ACE-I/ARB.

Conclusion

Using data from a large, integrated health system, we found that higher levels of ACR were associated with a higher likelihood of initiating ACE-I/ARB, thus albumuria testing may be helpful in prompting the initiation of ACE-I/ARBs among some individuals. However, even among those with the highest levels of ACR, many individuals who may have been eligible for treatment with ACE-I/ARB were not initiated on them. A similar trend was found for other methods of albuminuria testing including PCR and dipstick measurement. These results provide evidence that results from albuminuria testing change patient care, suggesting that adherence to albuminuria testing is a key step in optimal medical management.

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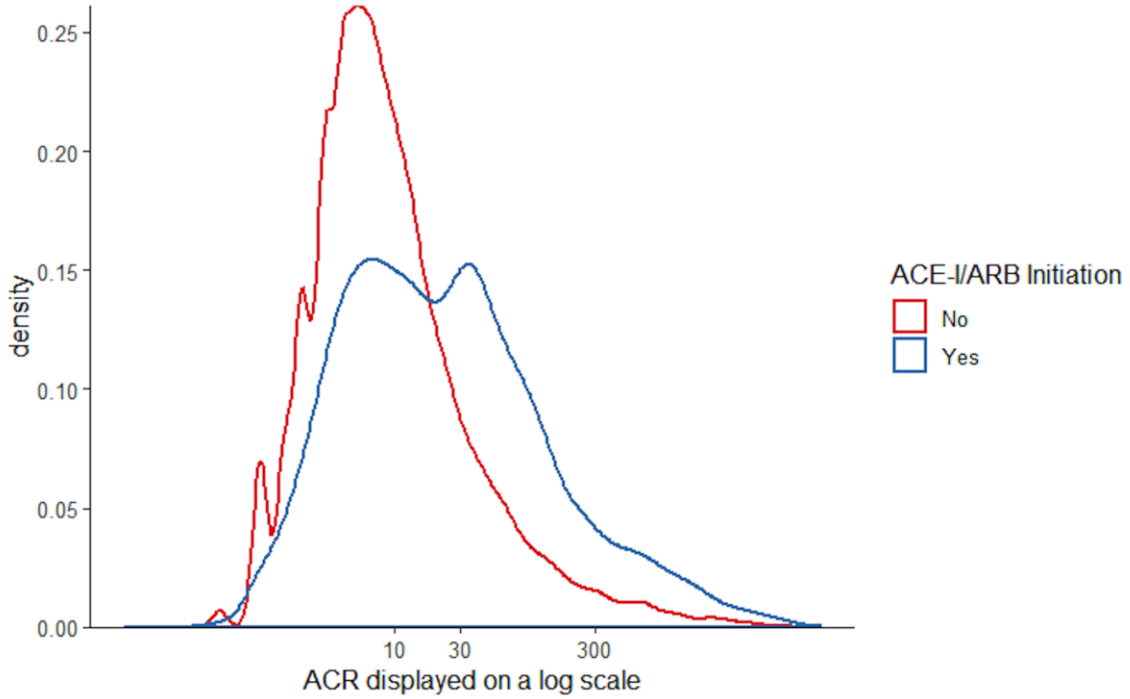
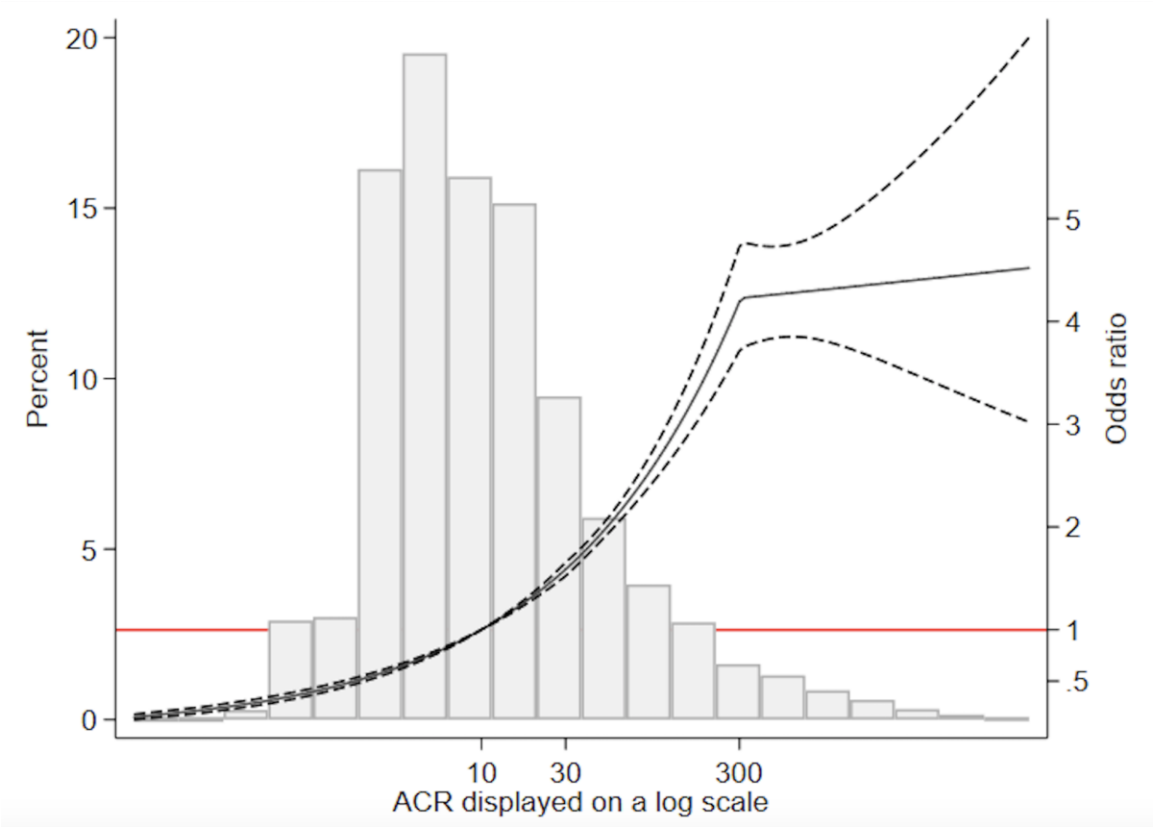
Figure 2- 1. Distribution of ACR stratified by ACE-I/ARB initiation within six months of the ACR test among individuals not on ACE-I/ARB at the time of the test (N=35,138), displayed on a log scale



Abbreviations: ACR, albumin-to-creatinine ratio; ACE-I/ARB: angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker

Figure 2- 2. Association* between ACR and initiation of ACE-I/ARB among individuals not on ACE-I/ARB at the time of the ACR test (N=35,138)



*Reference point at ACR 10 mg/g; adjusted for baseline age, sex, race/ethnicity, calendar year, systolic blood pressure, serum potassium, estimated glomerular filtration rate, diabetes, congestive heart failure, myocardial infarction, hypertension, use of statin, thiazide, calcium channel blocker, and beta blocker

Abbreviations: ACR, albumin-to-creatinine ratio; ACE-I/ARB: angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker

Table 2- 1. Characteristics of the patient cohort who received urine ACR measurement

Patient characteristics		Overall	Baseline use of ACE-I/ARB	
			Yes	No
Total number, N		67237	32099	35138
Urine ACR, median (IQR), mg/g		9 (4-26)	10 (4-29)	8 (4-23)
Age, mean (SD), years		60.5 (14.9)	62.7 (13.6)	58.4 (15.7)
Systolic blood pressure, mean (SD), mmHg		130 (16.4)	131 (16.8)	129 (15.9)
Potassium, mean (SD), mEq/L		4.3 (0.4)	4.3 (0.4)	4.3 (0.4)
eGFR, mean (SD), mL/min/1.73m^2		81 (24.1)	78 (23.2)	84 (24.4)
Female sex, N (%)		33696 (50.1)	15171 (47.3)	18525 (52.7)
Black race, N (%)		2526 (3.8)	1190 (3.7)	1336 (3.8)
Diabetes, N (%)		36722 (54.6)	17853 (55.6)	18869 (53.7)
Congestive heart failure, N (%)		4769 (7.1)	2969 (9.3)	1800 (5.1)
Hypertension, N (%)		49530 (73.7)	29979 (93.4)	19551 (55.6)
Myocardial infarction, N (%)		4073 (6.1)	2604 (8.1)	1469 (4.2)
Thiazide diuretics, N (%)		17623 (26.2)	11646 (36.3)	5977 (17.0)
Calcium channel blockers, N (%)		11504 (17.1)	7152 (22.3)	4352 (12.4)
Beta blockers, N (%)		23270 (34.6)	12990 (40.5)	10280 (29.3)
Statin, N (%)		31235 (46.5)	18173 (56.6)	13062 (37.2)
Calendar year, N (%)				
	2004-2008	16719 (24.9)	6785 (21.1)	9934 (28.3)
	2009-2013	20898 (31.1)	10192 (31.8)	10706 (30.5)
	2014-2018	29620 (44.1)	15122 (47.1)	14498 (41.3)

Abbreviations: ACR, albumin-to-creatinine ratio; IQR: interquartile range; SD, standard deviation; ACE-I/ARB: angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker; eGFR: estimated glomerular filtration rate

Table 2- 2. Associations of patient characteristics with the initiation of ACE-I/ARB among individuals not on ACE-I/ARB at the time of the ACR test (N=35,138)

Patient characteristics	Odds ratio (95% CI)
Urine ACR, per two-fold higher	
ACR below 30 mg/g	1.33 (1.30-1.37)
ACR between 30 and 300 mg/g	1.34 (1.29-1.40)
ACR above 300 mg/g	1.01 (0.93-1.10)
Age, per 10-year higher	0.86 (0.84-0.88)
Female sex	0.89 (0.83-0.94)
Black race	1.48 (1.29-1.70)
Systolic blood pressure, per 10-mmHg higher	1.32 (1.30-1.35)
Potassium, per mEq/L higher	1.24 (1.15-1.35)
eGFR, per 5-mL/min/1.73 m^2 higher	
eGFR below 30 mL/min/1.73 m^2	2.06 (1.63-2.60)
eGFR between 30 and 60 mL/min/1.73 m^2	1.09 (1.05-1.12)
eGFR above 60 mL/min/1.73 m^2	1.02 (1.01-1.03)
Diabetes	1.46 (1.38-1.56)
Congestive heart failure	0.80 (0.69-0.93)
Hypertension	1.95 (1.82-2.10)
Myocardial infarction	0.92 (0.79-1.08)
Thiazide diuretics	1.40 (1.30-1.52)
Calcium channel blockers	0.89 (0.81-0.97)
Beta blockers	0.82 (0.77-0.89)
Statin	1.33 (1.25-1.42)
Calendar year, 2004-2008 as reference	
2009-2013	0.78 (0.73-0.84)
2014-2018	0.60 (0.56-0.64)

Abbreviations: ACE-I/ARB: angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker; ACR, albumin-to-creatinine ratio; eGFR: estimated glomerular filtration rate; CI, confidence interval

Supplement

Table 2-S 1. International Classification of Disease, 9th and 10th Editions, Clinical Modification (ICD-9-CM, ICD-10-CM) Used to Define Disease Conditions

Disease condition	ICD-9-CM codes	ICD-10-CM codes
Diabetes	250.x	E10.x, E11.x, E13.x
Congestive heart failure	428.x	I50.x
Myocardial infarction	410.00, 410.0, 410.01, 410.02, 410.1, 410.10, 410.11, 410.12, 410.20, 410.2, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.4, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.7, 410.70, 410.71, 410.72, 410.8, 410.80, 410.81, 410.82, 410.9, 410.90, 410.91, 410.92, 411.0, 412, 429.7, 429.71, 429.79	I24.1, I25.2, I51.0, I21.x-I23.x
Hypertension	401.x-405.x	I10.x-I16.x

Table 2-S 2. Characteristics of the patient cohort who received urine PCR measurement

Patient characteristics		Overall	Baseline use of ACE-I/ARB	
			Yes	No
Total number, N		20104	10437	9667
Urine PCR, median (IQR), mg/g		110 (68-260)	116 (70-290)	100 (60-220)
Age, mean (SD), years		64.2 (16.5)	67.4 (13.9)	60.8 (18.3)
Systolic blood pressure, mean (SD), mmHg		130.8 (17.9)	132.9 (18.3)	128.4 (17.2)
Potassium, mean (SD), mEq/L		4.3 (0.4)	4.3 (0.4)	4.2 (0.4)
eGFR, mean (SD), mL/min/1.73m^2		61.1 (28.0)	57.2 (24.9)	65.2 (30.5)
Female sex, N (%)		11305 (56.2)	5473 (52.4)	5832 (60.3)
Black race, N (%)		475 (2.4)	237 (2.3)	238 (2.5)
Diabetes, N (%)		6710 (33.4)	4740 (45.4)	1970 (20.4)
Congestive heart failure, N (%)		2986 (14.9)	1860 (17.8)	1126 (11.7)
Hypertension, N (%)		15940 (79.3)	10008 (95.9)	5932 (61.4)
Myocardial infarction, N (%)		1874 (9.3)	1247 (12.0)	627 (6.5)
Thiazide diuretics, N (%)		4966 (24.7)	3441 (33.0)	1525 (15.8)
Calcium channel blockers, N (%)		5254 (26.1)	3340 (32.0)	1914 (19.8)
Beta blockers, N (%)		9246 (46.0)	5645 (54.1)	3601 (37.3)
Statin, N (%)		10128 (50.4)	6603 (63.3)	3525 (36.5)
Calendar year, N (%)				
	2004-2008	2583 (12.9)	1232 (11.8)	1351 (14.0)
	2009-2013	7493 (37.3)	3798 (36.4)	3695 (38.2)
	2014-2018	10028 (49.9)	5407 (51.8)	4621 (47.8)

Abbreviations: PCR, protein-to-creatinine ratio; IQR: interquartile range; SD, standard deviation; ACE-I/ARB: angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker; eGFR: estimated glomerular filtration rate

Table 2-S 3. Characteristics of the patient cohort who received urine dipstick measurement

Patient characteristics	Overall	Baseline use of ACE-I/ARB	
		Yes	No
Total number, N	141914	39664	102250
Urine dipstick measure, N (%)			
"Negative"	118951 (83.8)	31960 (80.6)	86991 (85.1)
"+"	19854 (14.0)	6489 (16.4)	13365 (13.1)
"++ or above"	3109 (2.2)	1215 (3.1)	1894 (1.9)
Age, mean (SD), years	54.2 (17.7)	63.1 (13.9)	50.8 (17.8)
Systolic blood pressure, mean (SD), mmHg	128 (17.1)	133 (17.8)	126 (16.4)
Potassium, mean (SD), mEq/L	4.2 (0.4)	4.3 (0.4)	4.2 (0.4)
eGFR, mean (SD), mL/min/1.73m^2	88 (23.9)	77 (22.9)	92 (23.1)
Female sex, N (%)	78052 (55.0)	19322 (48.7)	58730 (57.4)
Black race, N (%)	4850 (3.4)	1319 (3.3)	3531 (3.5)
Diabetes, N (%)	21701 (15.3)	13161 (33.2)	8540 (8.4)
Congestive heart failure, N (%)	6059 (4.3)	3493 (8.8)	2566 (2.5)
Hypertension, N (%)	66597 (46.9)	36758 (92.7)	29839 (29.2)
Myocardial infarction, N (%)	4951 (3.5)	2876 (7.3)	2075 (2.0)
Thiazide diuretics, N (%)	21544 (15.2)	13582 (34.2)	7962 (7.8)
Calcium channel blockers, N (%)	15446 (10.9)	8900 (22.4)	6546 (6.4)
Beta blockers, N (%)	30294 (21.4)	14998 (37.8)	15296 (15.0)
Statin, N (%)	38297 (27.0)	20143 (50.8)	18154 (17.8)
Calendar year, N (%)			
2004-2008	35432 (25.0)	7437 (18.8)	27995 (27.4)
2009-2013	42547 (30.0)	12094 (30.5)	30453 (29.8)
2014-2018	63935 (45.1)	20133 (50.8)	43802 (42.8)

Abbreviations: IQR: interquartile range; SD, standard deviation; ACE-I/ARB: angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker; eGFR: estimated glomerular filtration rate

Figure 2-S 1. Derivation of study cohort

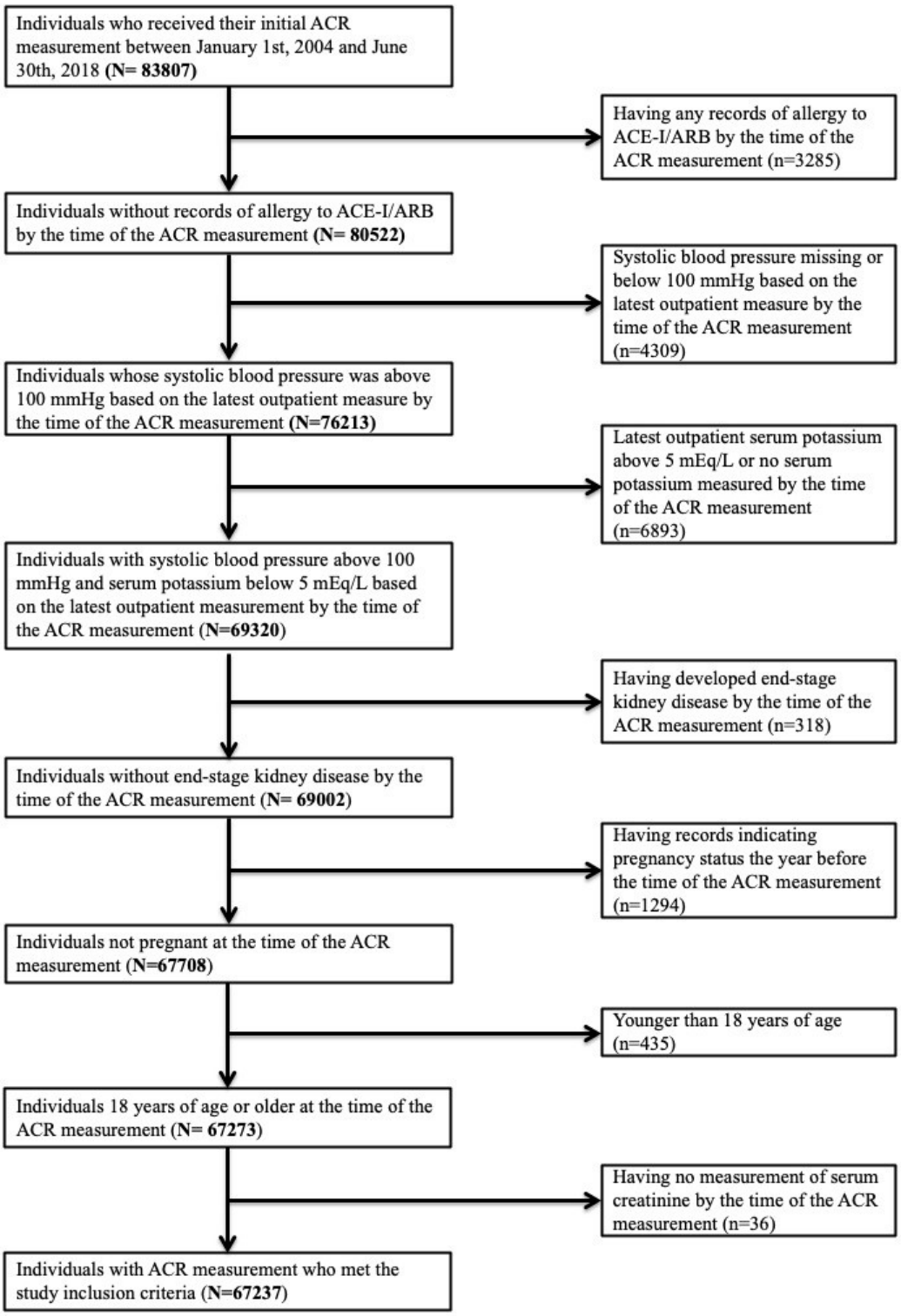
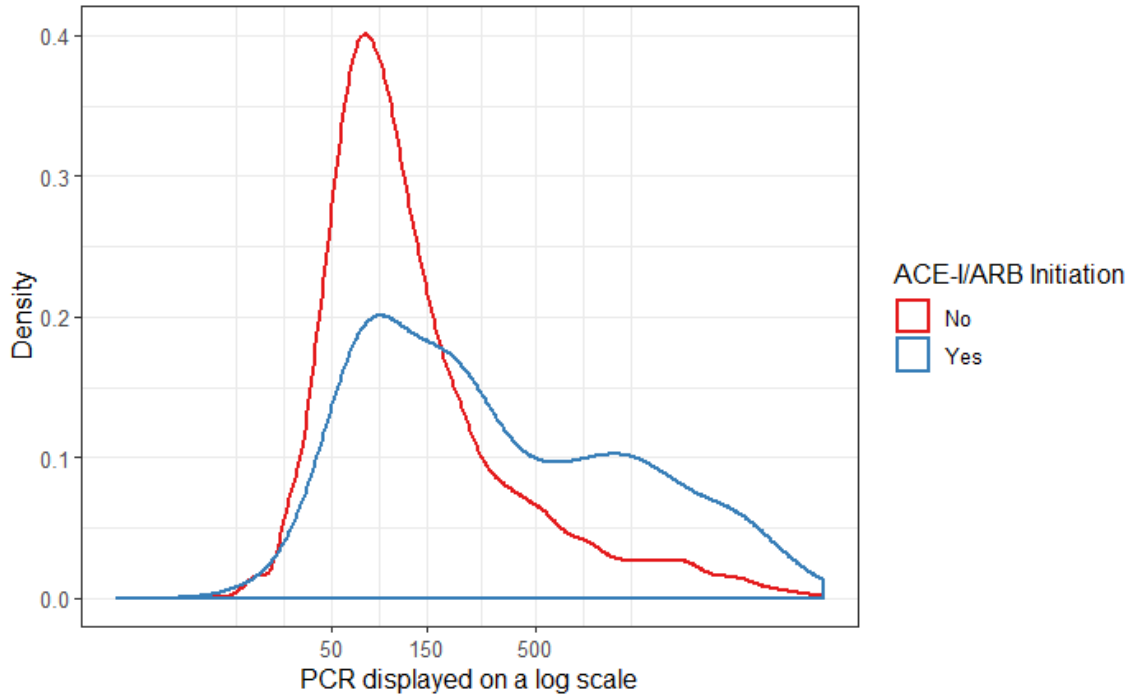
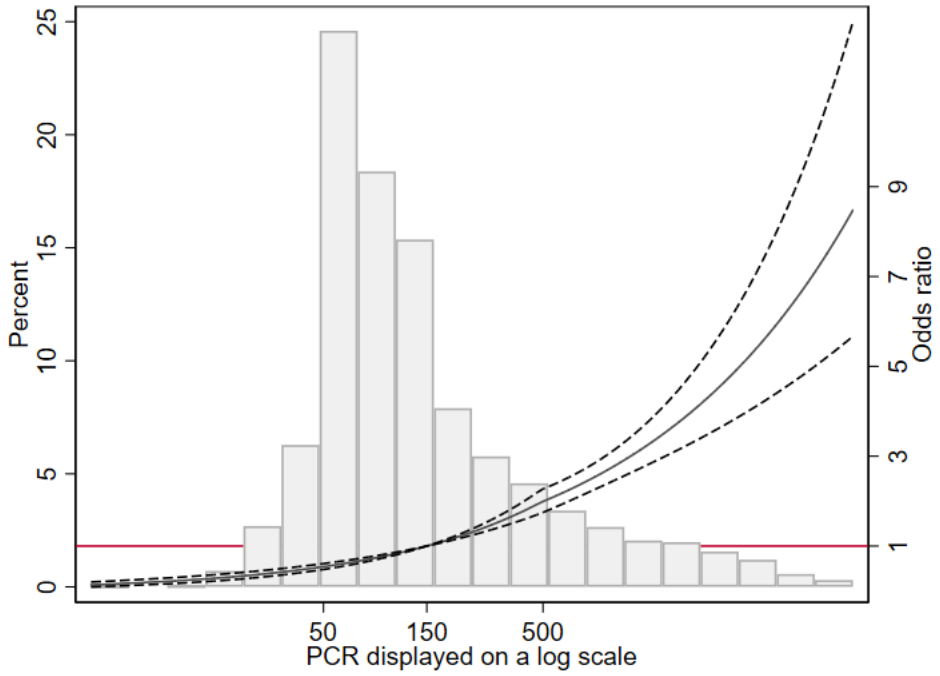


Figure 2-S 2. Distribution of PCR stratified by ACE-I/ARB initiation within six months of the PCR test among individuals not on ACE-I/ARB at the time of the test (N=9,667), displayed on a log scale



Abbreviations: PCR, protein-to-creatinine ratio; ACE-I/ARB: angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker

Figure 2-S 3. Association between PCR and initiation of ACE-I/ARB among individuals not on ACE-I/ARB at the time of the PCR test (N=9,667)



*Reference point at PCR 150 mg/g; adjusted for baseline age, sex, race/ethnicity, calendar year, systolic blood pressure, serum potassium, estimated glomerular filtration rate, diabetes, congestive heart failure, myocardial infarction, hypertension, use of statin, thiazide, calcium channel blocker, and beta blocker.

Abbreviations: PCR, protein-to-creatinine ratio; ACE-I/ARB: angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker

Chapter 3. Discontinuation of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Chronic Kidney Disease

Abstract

Objective: To assess the patterns of angiotensin converting enzyme inhibitors and angiotensin receptor blockers (ACE-I/ARB) discontinuation in the setting of chronic kidney disease (CKD) progression in real-world clinical practice.

Patients and Methods: We identified incident ACE-I/ARB users with a baseline estimated glomerular filtration rate (eGFR) ≥15mL/min/1.73m^2 and without end-stage renal disease in the Geisinger Health System between January 1, 2004 and December 31, 2015. We investigated the associations of CKD stage, hospitalizations with and without acute kidney injury (AKI), serum potassium, bicarbonate level, thiazide, and loop diuretic use with ACE-I/ARB discontinuation.

Results: Among the 53,912 ACE-I/ARB users, the mean age was 59.9 years and 50.6% were female. Over half discontinued ACE-I/ARB within 5 years of therapy initiation. The risk of ACE-I/ARB discontinuation increased with more advanced CKD stage. For example, patients who initiated ACE-I/ARB with CKD stage G4 (eGFR: 15-29ml/min/1.73m^2) were 2.09-times [95% CI: 1.87-2.34] more likely to discontinue therapy than those with eGFR≥90ml/min/1.73m^2. Potassium level>5.3mEq/L, systolic blood pressure≤90mmHg, bicarbonate level<22mmol/L, and intervening hospitalization – particularly AKI-related – were also strong risk factors for ACE-I/ARB discontinuation. Thiazide diuretic use was associated with lower risk, whereas loop diuretic use was associated with higher risk of discontinuation.

Conclusion: In a real-world cohort, discontinuation of ACE-I/ARB was common, particularly in patients with lower eGFR. Hyperkalemia, hypotension, low bicarbonate level, and

hospitalization (AKI-related, in particular) were associated with higher risk of ACE-I/ARB discontinuation. Additional studies are needed to evaluate the risk-benefit balance of discontinuing ACE-I/ARB in the setting of CKD progression.

Key words: discontinuation, antihypertensive, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, chronic kidney disease, estimated glomerular filtration rate

Abbreviations: ACE-I, angiotensin converting enzyme inhibitors; ACE-I/ARB, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or their combination; AKI, acute kidney injury; ARB, angiotensin receptor blockers; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KDIGO guideline, Kidney Disease Improving Global Outcomes guideline; OR, odds ratio

Introduction

Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) are first-line antihypertensives for individuals with albuminuria, and are among the few clinically-proven therapies to delay chronic kidney disease (CKD) progression in patients with albuminuria.[1–5] ACE-Is and ARBs may also provide benefits post myocardial infarction, with improvement in myocardial performance and survival compared with placebo.[6–11] On the other hand, ACE-Is, ARBs, or their combination (ACE-I/ARB) may predispose to hyperkalemia and acute kidney injury (AKI), risks that are particularly high among patients with low estimated glomerular filtration rate (eGFR) or albuminuria.[12,13]

Currently, there is equipoise in the safety and efficacy of ACE-I/ARB use in advanced CKD, which motivated ongoing clinical trials such as the STOP-ACEi trial.[14,15] The STOP-ACEi trial is a multi-center randomized controlled trial, which randomizes users of ACE-I/ARB with

advanced progressive CKD to either discontinue or continue to receive ACE-I/ARB.[14,15] Clinical guidelines reflect the uncertainty, and remain vague as to when ACE-I/ARB needs to be discontinued in patients with advanced CKD, leaving providers and patients to navigate these questions without clear scientific guidance. For example, the Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends "temporary discontinuation" of ACE-I/ARB "in people with a GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI"; yet also states "do not routinely discontinue [ACE-I/ARB therapy] in people with GFR <30 ml/min/1.73 m^2 as they remain nephroprotective".[16] Although clinical trials suggest the rate of discontinuation of ACE-Is and ARBs is low,[17] less is known about real-world practice in the setting of CKD progression.

The goal of this study was to describe ACE-I/ARB discontinuation patterns in a real-world setting using over ten years of data from a large, integrated healthcare delivery network, with a particular focus on patterns in the setting of CKD. As a secondary objective, we identified additional factors associated with ACE-I/ARB discontinuation, hypothesizing that hypotension, elevated potassium levels, low bicarbonate level, and recent AKI-related hospitalization would be among the strongest risk factors for discontinuing ACE-I/ARB therapy. Additionally, we assessed how ACE-I/ARB discontinuation was affected by concurrent use of loop and thiazide diuretics, two medication classes known to be associated with decreased risk of hyperkalemia.[18] Finally, among discontinued users, we assessed antecedent events as well as the frequency of restarting ACE-I/ARB within six months of therapy discontinuation.

Methods

Study design, population, and data source

We conducted a retrospective study using electronic health records (EHR) data from a community-based cohort receiving primary care in the Geisinger Health System. Geisinger Health System has 12 hospitals in central and northeastern Pennsylvania. This large, integrated EHR database combines patient-level information on demographic characteristics, outpatient prescriptions, problem lists, inpatient and outpatient encounters, and laboratory test results. Based on prescription records, we identified individuals who were first prescribed an ACE-I, an ARB, or the combination of both between January 1, 2004 and December 31, 2015 (**Supplemental eTable 1).** Baseline for each patient was the date of the initial ACE-I/ARB prescription, and follow-up was available until January 2017. Further inclusion criteria were age 18 years or older; having an outpatient measurement of serum creatinine, potassium, bicarbonate level, and systolic blood pressure within one year before baseline; and having baseline eGFR $\geq$15 mL/min/1.73 m^2 and no previous diagnosis of end-stage renal disease.

Outcome, exposure, and covariate definitions

The primary outcome was discontinuation after starting ACE-I/ARB therapy. Discontinuation was defined as a gap in therapy greater than 60 days. Switching to different medications within ACE-I, ARB, or between the two medication classes was not considered as discontinuation. Specifically, we classified discontinuation as the end date of a prescription if there was no subsequent prescription within 60 days and the individual continued to receive follow-up in the Geisinger system. We censored patients at the therapy end date if no subsequent outpatient encounter was observed more than 60 days after the end date.

CKD stage was defined based on the KDIGO guideline, with an eGFR $\geq$90, 60-89, 45-59, 30-44, 15-29, and $<$15 mL/min/1.73 m^2 classified as G1, G2, G3a, G3b, G4, and G5,

respectively.[16] The eGFR was estimated from outpatient serum creatinine levels using the CKD-EPI equation.[19] Baseline eGFR was the latest outpatient measure taken within one year prior to the initial ACE-I/ARB prescription. Time-dependent CKD stage was ascertained using time-updated outpatient measures of serum creatinine.

Other covariates included age at baseline, gender, race, initial class of therapy (i.e., ACE-I, ARB, or the combination of both), and calendar year of initial ACE-I/ARB prescription. Additionally, we defined both baseline and time-dependent variables for serum potassium, bicarbonate level, and systolic blood pressure using the latest outpatient measurement during the one-year period prior to initial ACE-I/ARB prescription and updated outpatient measures during the follow-up period, respectively. We also captured baseline and time-updated use of loop and thiazide diuretics using prescription records (**Supplemental eTable 1)**. Baseline comorbidities such as diabetes, congestive heart failure, and coronary artery disease were determined based on the presence of diagnostic codes prior to the initial prescription (**Supplemental eTable 2**). A binary variable was created to indicate "albuminuria testing", defined by whether a patient had an outpatient measure of albuminuria on or before the baseline date. We also defined a time-dependent "recent hospitalization" variable indicating hospitalization within the previous 30 days. For each hospitalization, we further classified it as AKI-related versus non-AKI-related based on diagnostic codes.

Statistical analysis

We described the baseline characteristics of the overall study cohort as well as stratified by baseline CKD stage. Cumulative incidence curves were used to depict time to discontinuation since initial ACE-I/ARB prescription by baseline CKD stage, accounting for the competing risk

of death. Fine-Gray competing risk regression models were constructed to quantify the associations of ACE-I/ARB discontinuation with CKD stage as well as other factors that may affect discontinuation, with death as a competing event.[20] We first ran a model (Model 1) that included the following baseline variables: CKD stage, drug class/classes of the initial prescription (ACE-I, ARB, the combination of ACE-I and ARB,), calendar year of initial prescription (2004-2007, 2008-2011, 2012-2015), age (18-44, 45-64, 65+), female sex, black race, diabetes, congestive heart failure, coronary artery disease, albuminuria testing, potassium level (≤3.5, 3.5-5, 5-5.3, >5.3 mEq/L), systolic blood pressure (≤90, 90-140, ≥140 mmHg), low bicarbonate level (<22 mmol/L), use of loop diuretics, and thiazide diuretics. Model 2 included the same variables except that CKD stage, potassium level, systolic blood pressure, low bicarbonate level, and use of loop and thiazide diuretics were captured as time-dependent variables to incorporate changes during the observation period. Model 2 also adjusted for the time-dependent variable of recent hospitalization status (no hospitalization, AKI-related hospitalization, non-AKI-related hospitalization within the previous 30 days).

Among discontinued users, we described the prevalence of the following risk factors preceding discontinuation: CKD progression (decline in eGFR ≥30% compared to the antecedent measure), hyperkalemia (serum potassium >5 mEq/L), recent hospitalizations with and without AKI, bicarbonate level <22 mmol/L, and systolic blood pressure ≤90 mmHg, stratified by CKD stage prior to discontinuation. We performed logistic regression to assess the associations of demographic and clinical characteristics with restarting therapy within six months of discontinuation.

Sensitivity analysis

We performed several sensitivity analyses. First, we defined discontinuation as a gap greater than 90 days without receiving ACE-I/ARB, and repeated the primary analyses. Second, we excluded individuals who were prescribed ACE-I/ARB at their first outpatient encounter in the Geisinger system. Finally, we evaluated the pattern of discontinuation across CKD stages of a comparison medication class, beta-blockers, to discern whether the observed associations were class-specific and not simply a marker of poor health.

Results

Study population

A total of 53,912 individuals from the Geisinger Health System met the inclusion criteria (**Figure 3-S 1**). The study population was 50.6% female and had a mean (SD) age of 59.9 (14.9) years. The majority (88.0%) of the initial prescriptions were for ACE-I, with 11.3% for ARB, and 0.7% for both (**Table 3-1**). At baseline, 23,069 (42.8%), 23,158 (43.0%), 5,123 (9.5%), 2,029 (3.8%), and 533 (1.0%) patients were classified as G1, G2, G3a, G3b, and G4 CKD stage, respectively. The proportion of patients initially prescribed ARBs was higher among those with more advanced baseline CKD stages.

Association between discontinuation and the severity of CKD

In total, 28,670 patients discontinued ACE-I/ARB therapy during follow-up. More advanced CKD stage at baseline was associated with greater risk of discontinuation (**Figure 3-1**; $P<.001$ for all comparisons between G2, G3a, G3b, G4, and G1). Based on the cumulative incidence of ACE-I/ARB discontinuation accounting for the competing risk of death, we estimated that 20.7% [95% confidence interval (CI): 20.2-21.3%], 22.9% [95% CI: 22.3-23.4%], 26.7% [95% CI: 25.4-27.9%], 30.1% [95% CI: 28.1-32.3%], and 45.3% [95% CI: 41.0-49.8%] had discontinued

ACE-I/ARB use by one year of therapy initiation among patients with G1, G2, G3a, G3b, and G4 CKD stage at baseline, respectively. These proportions rose to 46.8% [95% CI: 46.1-47.5%], 49.7% [95% CI: 49.0-50.4%], 58.8% [95% CI: 57.2-60.3%], 68.4% [95% CI: 65.9-70.8%], and 83.7% [95% CI: 79.5-87.4%] by five years after treatment initiation.

In adjusted analysis, more advanced CKD stage at baseline continued to be significantly associated with higher risk of discontinuation (hazard ratio (HR): 1.06 [95% CI: 1.03-1.09], 1.22 [95% CI: 1.17-1.28], 1.40 [95% CI: 1.32-1.49], and 2.09 [95% CI: 1.87-2.34] respectively for G2, G3a, G3b, and G4, compared with G1) (Model 1, **Table 3-2**). When CKD stage was treated as time-dependent, a similar pattern persisted but the effects were more pronounced, i.e. G2, G3a, G3b, and G4 yielded HRs of 1.08 [95% CI: 1.04, 1.11], 1.25 [95% CI: 1.19, 1.30], 1.45 [95% CI: 1.36, 1.55], and 2.43 [95% CI: 2.17, 2.72], respectively, compared with G1 (Model 2). Although we excluded patients with G5 CKD stage at baseline, some patients progressed to G5 during follow up, which was associated with a substantially elevated risk of discontinuation (HR: 4.62 [95% CI: 3.27, 6.52], compared with G1).

Other factors associated with discontinuation

AKI-related hospitalization was among the strongest risk factors of ACE-I/ARB discontinuation (HR: 7.10 [95% CI: 6.11-8.25]); non-AKI-related hospitalization also elevated the risk of discontinuation (HR: 4.54 [95% CI: 4.22-4.89]). High potassium levels (5-5.3, and >5.3 mEq/L) were associated with higher risk of discontinuation compared with potassium levels in the normal range (3.5-5 mEq/L). Similarly, low systolic blood pressure (≤90 mmHg) and low bicarbonate level (<22 mmol/L) were risk factors for discontinuation. Concurrent use of thiazide diuretics was associated with decreased risk of ACE-I/ARB discontinuation whereas loop

diuretics were associated with increased risk of discontinuation. There was no difference in risk of discontinuation between patients with an initial prescription of ACE-I and those initially prescribed ARB.

Events preceding discontinuation and restarting therapy within six months of discontinuation

Among the 28,670 patients who discontinued ACE-I/ARB use, the proportion with antecedent CKD progression, hyperkalemia, recent hospitalizations with and without AKI, bicarbonate level <22 mmol/L, and systolic blood pressure ≤90 mmHg increased from G1 to G5 (**Figure 3-2)**. Most patients who discontinued ACE-I/ARB at G1 or G2 stage did not manifest any of these risk factors before discontinuation; whereas the majority who discontinued at G4 or G5 stage experienced at least one of these risk factors prior to discontinuation.

There were 6,135 (21.4%) patients who restarted ACE-I/ARB within six months of discontinuation, and 632 (2.2%) patients who died within six months of discontinuation without restarting therapy. Patients who discontinued at G3a were more likely to restart ACE-I/ARB within 6 months of discontinuation (odds ratio (OR): 1.18 [95% CI: 1.07, 1.31]) whereas those who discontinued at G4 or G5 were less likely to restart (OR: 0.83 [95% CI: 0.69, 0.99]), compared with G1 (**Table 3-S 3**). No significant differences were detected between G1 and other G-stages. Patients who discontinued after a recent non-AKI-related hospitalization were more likely to restart therapy. Additionally, women were less likely to restart than men.

Sensitivity analysis

The sensitivity analyses using a 90-day gap as the threshold to define discontinuation and excluding individuals prescribed ACE-I/ARB at the first outpatient encounter yielded substantively similar findings.

Among 44,634 incident users of beta-blockers, there was a completely different pattern of time to discontinuation across CKD stages in comparison to ACE-I/ARB, with G1 stage showing the highest rate of discontinuation and other CKD stages showing fairly similar rates of discontinuation (**Figure 3-S 2**).

This study was approved by the Johns Hopkins University Institutional Review Board and the Geisinger Medical Center Institutional Review Board.

Discussion

Main findings

In this study of 53,912 incident users of ACE-I/ARB observed over a decade in a community-based health system, we estimated that the majority had a discontinuation in treatment by 5 years. There was no difference in risk of discontinuation between people initially prescribed an ACE-I compared to those prescribed an ARB, but there were strong associations of advanced CKD stages with therapy discontinuation, with patients with G4 disease (eGFR: 15-29 ml/min/1.73 m^2) more than twice as likely to discontinue therapy compared to people with eGFR ≥90 mL/min/1.73m^2. This pattern was specific to ACE-I and ARB therapy and not observed in incident beta-blocker users. We also observed that recent hospitalization, particularly hospitalization with AKI, was a strong risk factor for discontinuation. Our findings highlight how commonly ACE-Is and ARBs are discontinued among individuals with CKD, and suggest that post-hospitalization periods are critical junctures to re-evaluate appropriate ACE-I and ARB use. Given the associations with acidosis and thiazide diuretics, we propose that correcting acidosis and treating with thiazide diuretics may provide an opportunity to extend the duration of ACE-I/ARB therapy, although this requires formal testing.

Discontinuation of treatment has been relatively understudied compared to the initiation and escalation of a given therapy. Among patients with CKD, the risk of treatment discontinuation or treatment withholding may be particularly high. For example, the utilization of coronary angiography is lower in patients with CKD compared to those without, which may be due to perceived uncertainties of the procedure's risks and benefits in the CKD population.[21,22] A previous study showed that patients who initiated ACE-I/ARB therapy for renal indications were more likely to discontinue therapy than those who initiated ACE-I/ARB therapy for other indications.[23] Although our study cannot tease out the reason for ACE-I/ARB prescription, it does suggest that patients with lower GFR take therapy for shorter amounts of time, which may diminish the beneficial effects of ACE-I/ARB use in CKD. Indeed, the KDIGO guideline does not recommend routine discontinuation of ACE-I and ARB in patients with GFR < 30 mL/min/1.73 m^2.[16] It is also worth noting that our study only revealed the pattern among individuals who initiated ACE-I/ARB; there are many patients with CKD who would benefit from ACE-I/ARB use but never initiated the therapy.

Our results expand upon existing data on ACE-I and ARB discontinuation rates, which largely originated from clinical trials.[24] A meta-analysis of 22,542 patients without heart failure across eight randomized controlled trials showed a pooled discontinuation rate of 6.5% and 4.9% for ACE-I and ARB users, respectively, over an average of 3.4 years of follow-up.[17] In comparison, our study reflected real-world ACE-I/ARB use, had a greater representation of patients with advanced CKD, and observed a much higher rate of discontinuation, with over 50% ACE-I/ARB users discontinuing therapy by 5 years. Our discontinuation rate was consistent with a population-based study in the UK, which showed that 56.8% discontinued ACE-I use at 5 years post-initiation.[23]

An interesting finding in our study was that thiazide diuretics were associated with lower risk of ACE-I/ARB discontinuation. In contrast, loop diuretics were associated with higher risk of discontinuation. This may be due to the fact that thiazide diuretics have greater effect on lowering serum potassium than loop diuretics, thus preventing hyperkalemia;[25–30] whereas loop diuretics may result in greater water diuresis, predisposing to AKI. We also found that lower bicarbonate level was a risk factor for ACE-I/ARB discontinuation. These results provide important insights for clinical practice, suggesting that thiazide diuretics and/or correction of metabolic acidosis may prolong the safe use of ACE-I/ARB. On the other hand, the associations may simply reflect the sicker patient population that develops metabolic acidosis and requires loop diuretics.

There are several limitations to our study. First, our study population was primarily white, limiting generalizability to other races/ethnicities. Second, ACE-I/ARB use was ascertained using prescription data and we did not validate whether these medications were actually dispensed or taken. Thus, our study demonstrates prescription patterns in clinical practice rather than patient adherence to medication. Finally, we do not know the reason a medication was discontinued, and patterns cannot be interpreted as causal.

Strengths of our study included the large community-based cohort with over a decade of follow-up, which provided sufficient power and a high level of precision in study results. Clinical measures were ascertained not only at baseline, but also throughout the follow-up period. We demonstrated robustness of our findings through multiple sensitivity analyses including using a more conservative threshold of medication discontinuation, and comparing patterns to a negative control class of medications.

Conclusion

In conclusion, among 53,912 incident users of ACE-I/ARB in a large community-based cohort, over half discontinued therapy within 5 years, with higher risks of discontinuation among those with more advanced CKD. Risk of discontinuation was particularly high subsequent to AKI-related hospitalization. Use of thiazide diuretics was associated with a lower risk of ACE-I/ARB discontinuation whereas loop diuretics were associated with a higher risk of discontinuation. Our findings suggest a need for more precise assessment of risk-benefit balance of ACE-I/ARB discontinuation in patients with advanced CKD, as both overuse and underuse can be harmful to health outcomes.

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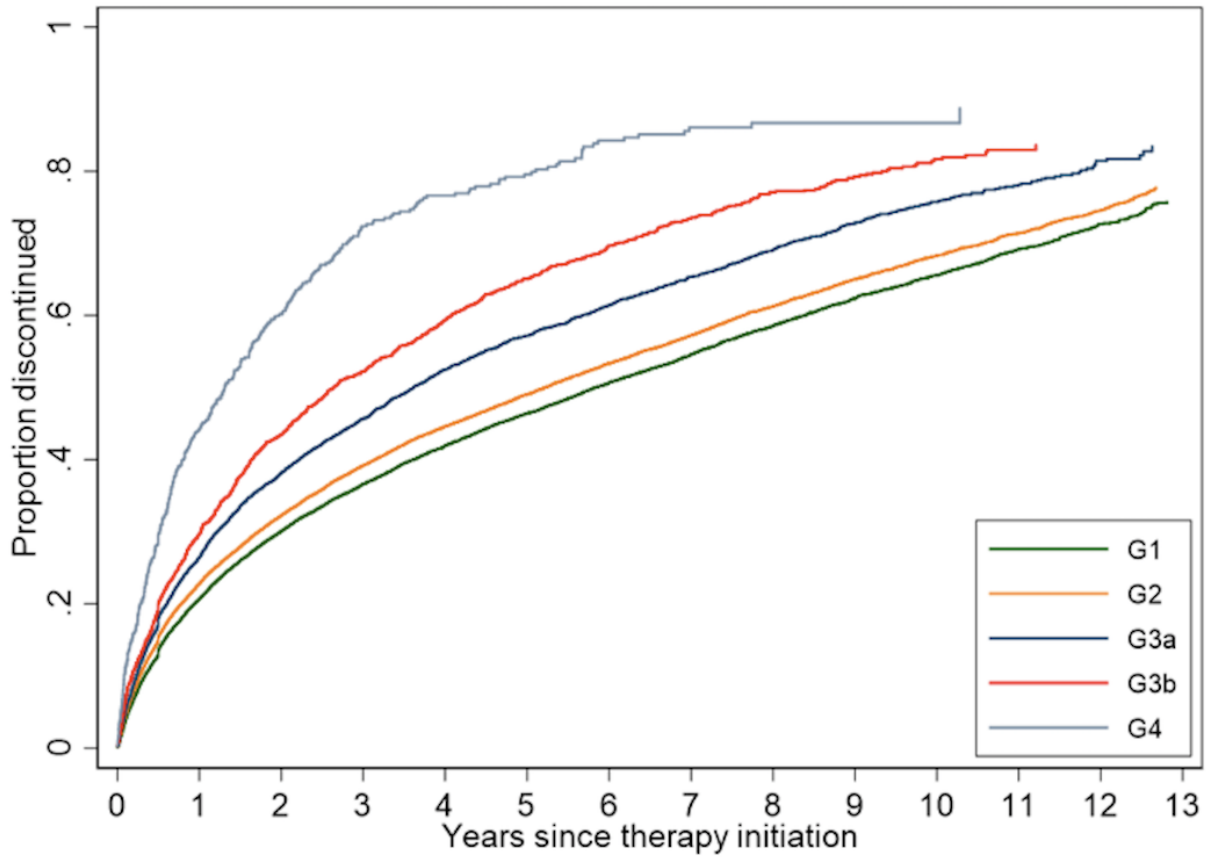
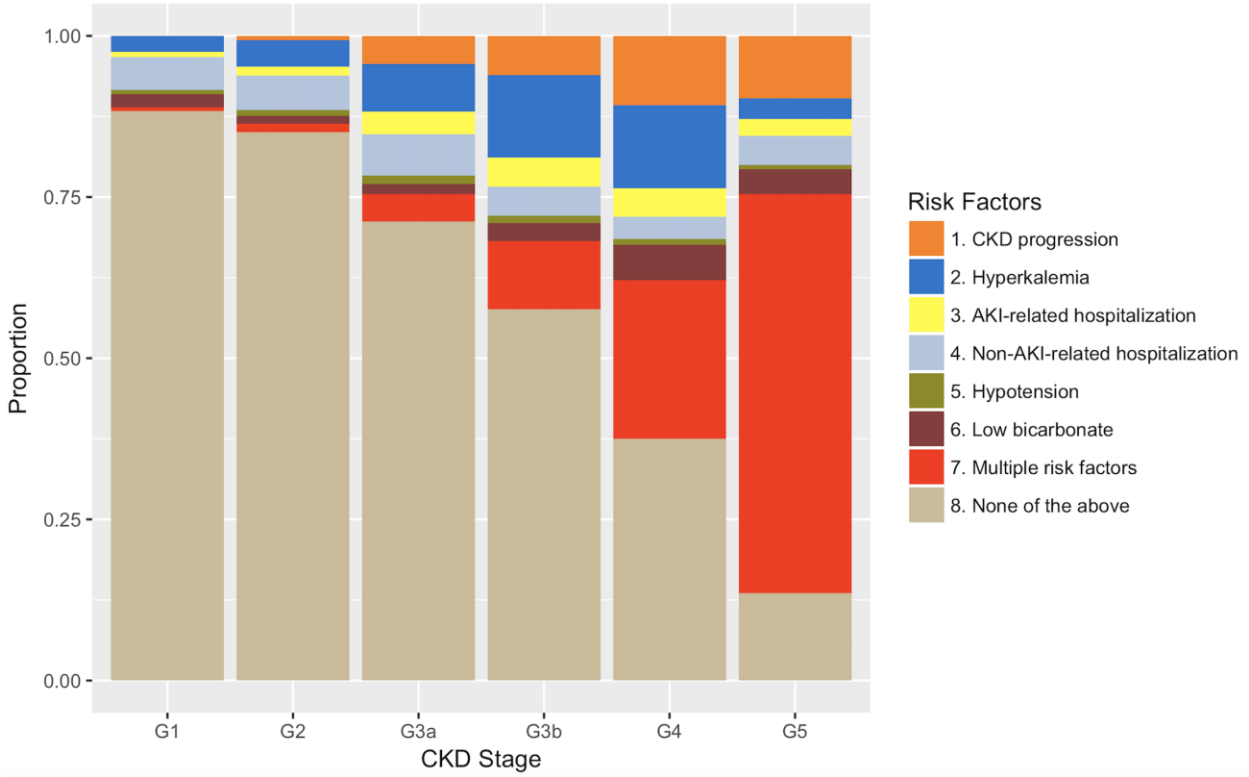
Figure 3- 1. Discontinuation of ACE-I/ARB among incident users, by CKD stage at baseline



CKD stage at baseline	Number of patients initiating ACE-I/ARB	Number of patients who discontinued during follow up	Time from initial prescription to discontinuation, in years		
			P25	Median	P75
G1	23069	11568	1.38	5.73	12.36
G2	23158	12400	1.18	5.08	11.42
G3a	5123	3039	0.87	3.46	8.79
G3b	2029	1276	0.73	2.49	6.34
G4	533	387	0.38	1.26	2.97
TOTAL	53912	28670	1.17	4.94	11.43

Abbreviations: ACE-I/ARB, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or their combination; CKD, chronic kidney disease

Figure 3- 2. Events preceding discontinuation of ACE-I/ARB, by CKD stage



Abbreviations: ACE-I/ARB, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or their combination; CKD, chronic kidney disease; AKI, acute kidney injury

Table 3- 1. Baseline characteristics of incident users of ACE-I/ARB by baseline CKD stage in the Geisinger health system, N (%)[a]

CKD Stage at treatment initiation	Overall	G1	G2	G3a	G3b	G4
	N=53912	N=23069 (42.8%)	N=23158 (43.0%)	N=5123 (9.5%)	N=2029 (3.8%)	N=533 (1.0%)
Drug class						
ACE-I	47472 (88.0)	20906 (90.6)	20314 (87.7)	4296 (83.9)	1594 (78.6)	362 (67.9)
ARB	6068 (11.3)	2021 (8.8)	2703 (11.7)	784 (15.3)	408 (20.1)	152 (28.5)
ACE-I and ARB	372 (0.7)	142 (0.6)	141 (0.6)	43 (0.8)	27 (1.3)	19 (3.6)
Calendar year						
2004-2007	18103 (33.6)	6834 (29.6)	8094 (35.0)	2078 (40.6)	867 (42.7)	230 (43.2)
2008-2011	18504 (34.3)	8448 (36.6)	7681 (33.2)	1552 (30.3)	638 (31.4)	185 (34.7)
2012-2015	17305 (32.1)	7787 (33.8)	7383 (31.9)	1493 (29.1)	524 (25.8)	118 (22.1)
Age group						
18-44	8347 (15.5)	6939 (30.1)	1232 (5.3)	102 (2.0)	44 (2.2)	30 (5.6)
45-64	24580 (45.6)	13437 (58.3)	9819 (42.4)	937 (18.3)	284 (14.0)	103 (19.3)
65+	20985 (38.9)	2693 (11.7)	12107 (52.3)	4084 (79.7)	1701 (83.8)	400 (75.1)
Female	27256 (50.6)	10846 (47.0)	11822 (51.1)	3031 (59.2)	1268 (62.5)	289 (54.2)
Black race	1319 (2.5)	893 (3.9)	343 (1.5)	57 (1.1)	15 (0.7)	11 (2.1)
Diabetes	16641 (30.9)	7798 (33.8)	6245 (27.0)	1594 (31.1)	776 (38.3)	228 (42.8)
Congestive heart failure	3991 (7.4)	791 (3.4)	1768 (7.6)	794 (15.5)	488 (24.1)	150 (28.1)
Coronary artery disease	9823 (18.2)	2530 (11.0)	4795 (20.7)	1533 (29.9)	772 (38.1)	193 (36.2)
Measured albuminuria	14222 (26.4)	6692 (29.0)	5420 (23.4)	1384 (27.0)	577 (28.4)	149 (28.0)
Potassium level						
3.5 mEq/L or lower	2039 (3.8)	918 (4.0)	844 (3.6)	193 (3.8)	68 (3.4)	16 (3.0)
3.5-5 mEq/L	49764 (92.3)	21573 (93.5)	21449 (92.6)	4608 (90.0)	1726 (85.1)	408 (76.6)
5-5.3 mEq/L	1573 (2.9)	460 (2.0)	674 (2.9)	219 (4.3)	158 (7.8)	62 (11.6)
Above 5.3 mEq/L	536 (1.0)	118 (0.5)	191 (0.8)	103 (2.0)	77 (3.8)	47 (8.8)
Systolic blood pressure						
90 mmHg or lower	221 (0.4)	67 (0.3)	76 (0.3)	42 (0.8)	26 (1.3)	10 (1.9)
90-140 mmHg	24370 (45.2)	10388 (45.0)	10015 (43.3)	2562 (50.0)	1126 (55.5)	279 (52.4)
140 mmHg or above	29321 (54.4)	12614 (54.7)	13067 (56.4)	2519 (49.2)	877 (43.2)	244 (45.8)
Bicarbonate lower than 22mmol/L	1022 (1.9)	456 (2.0)	290 (1.3)	101 (2.0)	89 (4.4)	86 (16.1)
Loop diuretic use	6016 (11.2)	1509 (6.5)	2570 (11.1)	1083 (21.1)	641 (31.6)	213 (40.0)
Thiazide diuretic use	14343 (26.6)	6059 (26.3)	6383 (27.6)	1311 (25.6)	457 (22.5)	133 (25.0)

[a]ACE-I = angiotensin converting enzyme inhibitors; ACE-I/ARB = angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or their combination; ARB = angiotensin receptor blockers; CKD = chronic kidney disease

Table 3- 2. Association of demographic and clinical factors with discontinuation of ACE-I/ARB, subhazard ratio and 95% confidence interval[a,b]

Demographic and Clinical Factors	Model 1	Model 2
CKD stage (referent: G1)		
G2	**1.06 (1.03, 1.09)**	**1.08 (1.04, 1.11)**
G3a	**1.22 (1.17, 1.28)**	**1.25 (1.19, 1.30)**
G3b	**1.40 (1.32, 1.49)**	**1.45 (1.36, 1.55)**
G4	**2.09 (1.87, 2.34)**	**2.43 (2.17, 2.72)**
G5[c]		**4.62 (3.27, 6.52)**
Drug class (referent: ACE-I alone)		
ACE-I and ARB	0.95 (0.84, 1.08)	0.93 (0.80, 1.07)
ARB alone	0.99 (0.95, 1.02)	0.99 (0.95, 1.03)
Calendar year (referent: 2004-2007)		
2008-2011	**1.14 (1.10, 1.17)**	**1.13 (1.09, 1.16)**
2012-2015	**1.24 (1.20, 1.28)**	**1.20 (1.16, 1.24)**
Age group (referent: 18-44)		
45-64	**0.82 (0.79, 0.85)**	**0.80 (0.77, 0.83)**
65+	**0.94 (0.90, 0.98)**	**0.82 (0.78, 0.85)**
Female	**1.15 (1.13, 1.18)**	**1.15 (1.12, 1.18)**
Black race	1.07 (0.99, 1.16)	1.07 (0.99, 1.16)
Diabetes	0.99 (0.96, 1.03)	**0.94 (0.91, 0.98)**
Congestive heart failure	1.00 (0.95, 1.05)	**0.79 (0.74, 0.84)**
Coronary artery disease	**1.15 (1.11, 1.18)**	**1.07 (1.03, 1.10)**
Measured albuminuria	**0.93 (0.89, 0.96)**	**0.96 (0.92, 0.99)**
Potassium level (referent: 3.5-5 mEq/L)		
3.5 mEq/L or lower	1.04 (0.98, 1.11)	**1.12 (1.03, 1.21)**
5-5.3 mEq/L	**1.09 (1.02, 1.16)**	1.06 (0.99, 1.14)
Above 5.3 mEq/L	**1.24 (1.11, 1.38)**	**1.94 (1.74, 2.17)**
Systolic blood pressure (referent: 90-140 mmHg)		
90 mmHg or lower	**1.23 (1.01, 1.49)**	**1.84 (1.57, 2.15)**
140 mmHg or above	**0.93 (0.90, 0.95)**	**1.07 (1.04, 1.10)**
Bicarbonate lower than 22mmol/L	**1.14 (1.05, 1.24)**	**1.11 (1.01, 1.22)**
Loop diuretic use	**1.14 (1.09, 1.18)**	**1.34 (1.29, 1.39)**
Thiazide diuretic use	**0.90 (0.88, 0.93)**	**0.85 (0.82, 0.87)**
Hospitalization status (referent: no hospitalization)		
Non-AKI-related	-	**4.54 (4.22, 4.89)**
AKI related	-	**7.10 (6.11, 8.25)**

[a] ACE-I = angiotensin converting enzyme inhibitors; ACE-I/ARB = angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or their combination; AKI = acute kidney injury; ARB = angiotensin receptor blockers; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate. [b]Shaded fields indicate time-dependent form of the corresponding variables. [c]Patients with CKD G5 stage at baseline were excluded but some patients progressed to G5 after therapy initiation.

Supplement

Table 3-S 1. Drug products included in the analysis

(a) Angiotensin converting enzyme inhibitors
accupril
accuretic
aceon
altace
amlodipine besy-benazepril hcl
benazepril hcl
benazepril-hydrochlorothiazide
capoten
capozide
captopril
captopril-hydrochlorothiazide
enalapril
enalapril mal-diltiazem malate
enalapril maleate
enalapril maleate-felodipine
enalapril-hydrochlorothiazide
fosinopril sodium
fosinopril sodium-hctz
lexxel
lisinopril & diet manage prod
lisinopril
lisinopril-hctz
lisinopril-hydrochlorothiazide
lotensin
lotensin hct
lotrel
mavik
moexipril hcl
moexipril-hydrochlorothiazide
monopril
monopril hct
perindopril erbumine
prinivil
prinzide
quinapril
quinapril hcl
quinapril-hydrochlorothiazide
quinaretic
ramipril
tarka
trandolapril

trandolapril-verapamil hcl
uniretic
univasc
vaseretic
vasotec
zestoretic
zestril

(b) Angiotensin receptor blockers
amlodipine besylate-valsartan
amlodipine-olmesartan
amlodipine-valsartan-hctz
atacand
atacand hct
avalide
avapro
azilsartan medoxomil
azilsartan-chlorthalidone
azor
benicar
benicar hct
candesartan cilexetil
candesartan cilexetil-hctz
cozaar
diovan
diovan hct
edarbi
edarbyclor
entresto
eprosartan mesylate
eprosartan mesylate-hctz
exforge
exforge hct
hyzaar
Irbesartan
irbesartan-hydrochlorothiazide
losartan
losartan potassium
losartan potassium-hctz
micardis
micardis hct
olmesartan medoxomil
olmesartan medoxomil-hctz
olmesartan-amlodipine-hctz

sacubitril-valsartan
telmisartan
telmisartan-amlodipine
telmisartan-hctz
teveten
teveten hct
tribenzor
twynsta
valsartan
valsartan-hydrochlorothiazide
valturna

(c) Beta blockers
acebutolol hcl
atenolol
atenolol-chlorthalidone
betapace
betapace af
betaxolol hcl
bisoprolol
bisoprolol fumarate
bisoprolol fumarate-hctz
bisoprolol-hydrochlorothiazide
blocadren
bystolic
carvedilol & diet manage prod
carvedilol
carvedilol phosphate
coreg
corgard
corzide
dutoprol
inderal
inderide
innopran
kerlone
labetalol
labetalol hcl
levatol
lopressor
lopressor hct
metoprolol & diet manage prod
metoprolol
metoprolol succinate

metoprolol tartrate
metoprolol
metoprolol-hctz
metoprolol-hydrochlorothiazide
nadolol
nadolol-bendroflumethiazide
nebivolol hcl
normodyne
pindolol
propranolol hcl
propranolol-hctz
sectral
sorine
sotalol
sotalol hcl (af)
sotalol hcl
tenoretic
tenormin
timolide
timolol maleate
timolol-hydrochlorothiazide
toprol
trandate
visken
zebeta
ziac

(d) Loop diuretics
bumetanide
bumex
edecrin
furosemide
lasix

(e) Thiazide diuretics
accuretic
aldoril
aliskiren-amlodipine-hctz
aliskiren-hydrochlorothiazide
amlodipine-valsartan-hctz
apresazide
atacand hct
atenolol-chlorthalidone

avalide
azilsartan-chlorthalidone
benazepril-hydrochlorothiazide
bendroflumethiazide
benicar hct
bisoprolol fumarate-hctz
bisoprolol-hydrochlorothiazide
candesartan cilexetil-hctz
capozide
captopril-hydrochlorothiazide
chlorothiazide
clonidine-chlorthalidone
clorpres
corzide
diovan hct
diuril
dutoprol
edarbyclor
enalapril-hydrochlorothiazide
enduron
enduronyl
enduronyl forte
esidrix
exforge hct
fosinopril sodium-hctz
hydralazine & reserpine & hctz
hydralazine-hctz
hydrochlorothiazide
hyzaar
indapamide
inderide
irbesartan-hydrochlorothiazide
lisinopril-hctz
lisinopril-hydrochlorothiazide
lopressor hct
losartan potassium-hctz
lotensin hct
lozol
methyclothiazide
methyldopa-hydrochlorothiazide
metolazone
metoprolol-hctz
metoprolol-hydrochlorothiazide
micardis hct

microzide
moexipril-hydrochlorothiazide
monopril hct
mykrox
nadolol-bendroflumethiazide
olmesartan medoxomil-hctz
olmesartan-amlodipine-hctz
prinzide
propranolol-hctz
quinapril-hydrochlorothiazide
quinaretic
reserpine-hydralazine-hctz
ser-ap-es
tekturna hct
telmisartan-hctz
tenoretic
timolide
tribenzor
uniretic
valsartan-hydrochlorothiazide
vaseretic
zaroxolyn
zestoretic
ziac

Table 3-S 2. International classification of disease, 9th and 10th editions, clinical modification (ICD-9-CM, ICD-10-CM) used to define disease conditions

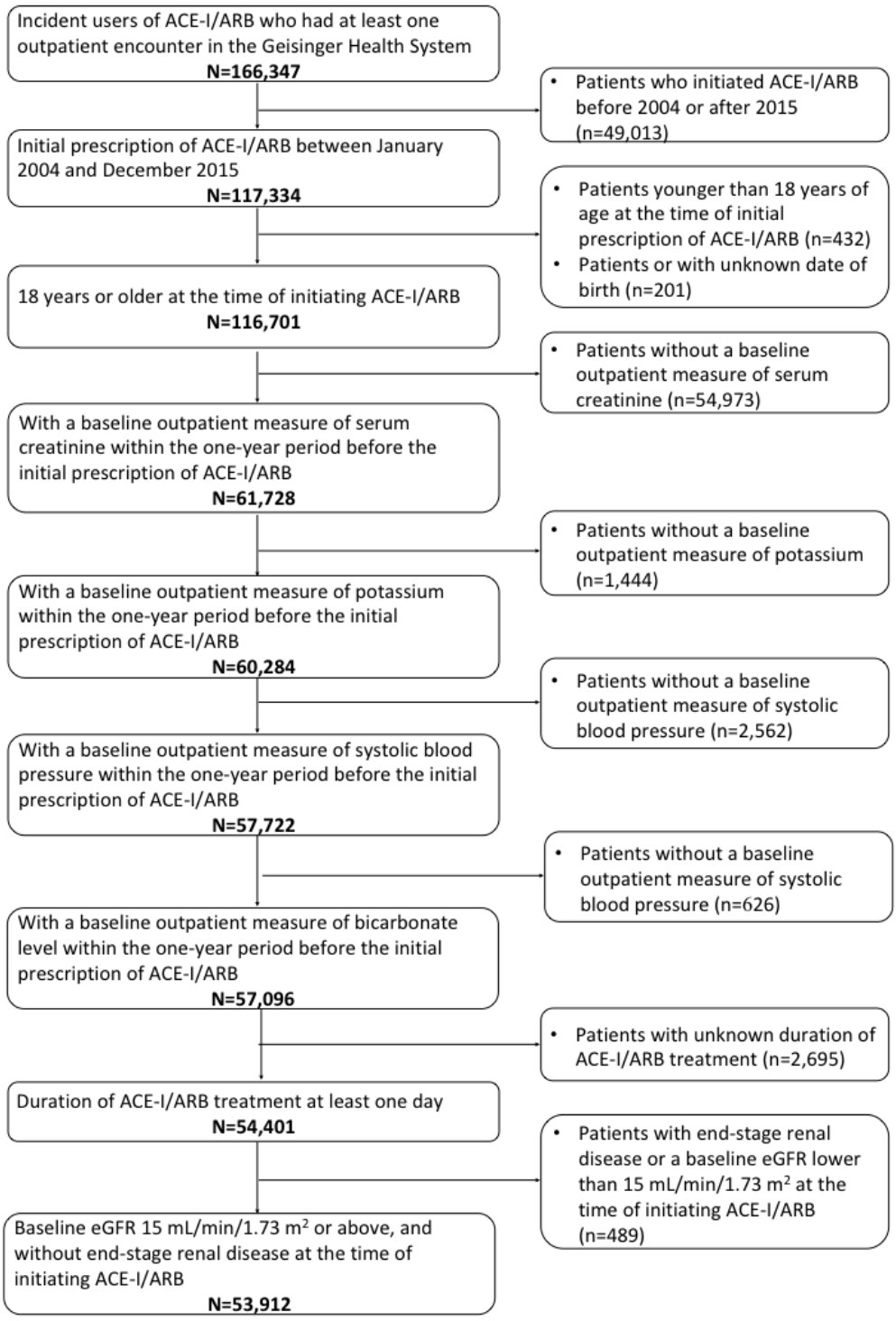
Disease Conditions	ICD-9-CM codes	ICD-10-CM codes
Diabetes	250.x	E10.x, E11.x, E13.x
Congestive heart failure	428.x	I50.x
Coronary artery disease	410.x, 411.0, 411.8x, 412, 414.x, 36.1x	I21.x, I22.x, I23.x, I24.x, I25.x
Acute kidney injury	584.x	N17.x

Table 3-S 3. Associations between clinical and demographic factors and restarting ACE-I/ARB within six months of therapy discontinuation[a]

Demographic and Clinical Factors		Odds Ratio (95% CI)
CKD Stage (referent: G1)		
	G2	1.04 (0.96, 1.12)
	G3a	1.18 (1.07, 1.31)
	G3b	1.11 (0.97, 1.26)
	G4 or G5	0.83 (0.69, 0.99)
Hospitalization (referent: no hospitalization)		
	Non-AKI-related	1.22 (1.09, 1.37)
	AKI-related	1.15 (0.97, 1.36)
Hypotension		0.80 (0.62, 1.03)
Low bicarbonate level		0.98 (0.83, 1.16)
Progression		1.09 (0.92, 1.29)
Hyperkalemia		1.07 (0.96, 1.20)
Age group (referent: 18-44)		
	45-64	1.20 (1.10, 1.31)
	65+	1.13 (1.02, 1.25)
Female		0.92 (0.87, 0.97)
Black race		1.20 (1.00, 1.44)

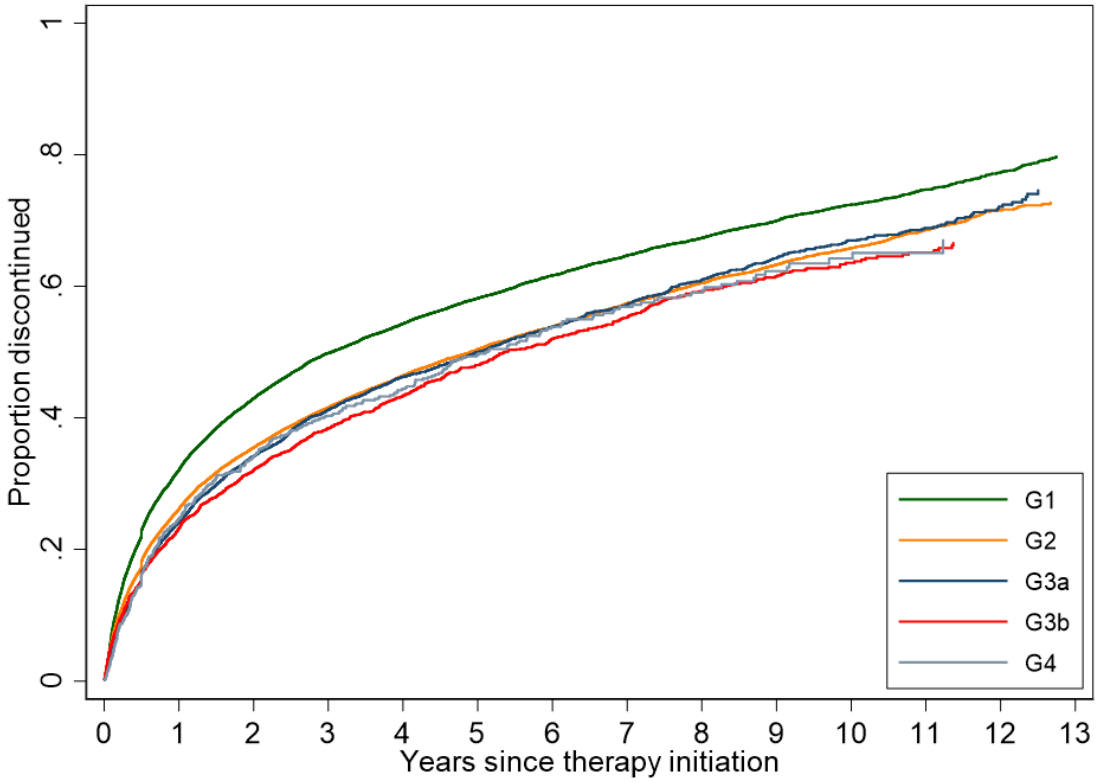
[a]ACE-I/ARB = angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or their combination; CKD = chronic kidney disease

Figure 3-S 1. Derivation of study cohort



Abbreviations: ACE-I/ARB, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or their combination; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Figure 3-S 2. Time to discontinuation of beta-blockers since therapy initiation, by baseline CKD stage



Abbreviations: CKD, chronic kidney disease

Chapter 4. Association Between Renin-angiotensin System Blockade Discontinuation And All-cause Mortality Among People With Low Estimated Glomerular Filtration Rate

Abstract

IMPORTANCE: It is uncertain whether and when angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) should be discontinued in individuals with low estimated glomerular filtration rate (eGFR).

OBJECTIVE: To investigate the association of ACE-I/ARB discontinuation after eGFR declines to below 30 ml/min/1.73m^2 with the risk of mortality, major adverse cardiovascular events (MACE), and end-stage kidney disease (ESKD).

DESIGN: Retrospective, propensity-score matched cohort study.

SETTING: An integrated health care system serving rural areas of central and northeastern Pennsylvania.

PARTICIPANTS: 3909 adults who initiated ACE-I/ARB between 2004 and 2018 and had an eGFR decline to below 30 ml/min/1.73m^2 during treatment, with follow up until January 25, 2019.

EXPOSURES: Individuals were classified based on whether they discontinued ACE-I/ARB within six months after the eGFR decline to below 30 ml/min/1.73m^2.

MAIN OUTCOMES AND MEASURES: We assessed the association between ACE-I/ARB discontinuation and mortality over the subsequent five years using multivariable Cox proportional hazards regression models, adjusting for patient characteristics at the

time of the eGFR decline in a propensity-score matched sample. Secondary outcomes included MACE and ESKD.

RESULTS: Of the 3909 ACE-I/ARB users with an eGFR decline to below 30 ml/min/1.73m^2, 2406 (62%) were female and the mean (SD) age was 73.7 (12.6) years. There were 1235 individuals who discontinued ACE-I/ARB within six months after eGFR decline and 2674 individuals who did not. A total of 434 (35.1%) and 786 (29.4%) individuals died over a median follow-up of 2.9 years among those with and without ACE-I/ARB discontinuation, respectively. In the propensity-score matched sample of 2410 individuals, ACE-I/ARB discontinuation was associated with a higher risk of mortality (HR: 1.39 [95% CI: 1.20-1.60]) and MACE (HR: 1.37 [95% CI: 1.20-1.56]), but no statistically significant difference in the risk of ESKD (HR: 1.19 [95% CI: 0.86-1.65]).

CONCLUSIONS AND RELEVANCE: Our findings provide evidence that continuing ACE-I/ARB in patients with declining kidney function may provide cardiovascular benefit without excessive harm of ESKD.

Introduction

Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) are the mainstays of therapy for hypertension, albuminuric chronic kidney disease (CKD), heart failure with reduced ejection fraction, and coronary artery disease.[1–6] However, the potential benefits of ACE-I/ARB therapy must be weighed against the potential risks, which include acute, largely hemodynamic reductions in estimated glomerular filtration rates (eGFR), hyperkalemia, and acute kidney injury (AKI).[4,7,8] The risks of these adverse events are particularly relevant in individuals with lower eGFR. In

real-world studies, over half of the individuals initiating ACE-I/ARB discontinued within 5 years after the initial prescription, with discontinuation increasingly common with more advanced CKD stage.[9,10]

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest "temporary discontinuation" of ACE-I/ARB in those with a GFR <60 ml/min/1.73m^2 (GFR categories G3a-G5) "who have serious intercurrent illness that increases the risk of AKI"; but also emphasize to "not routinely discontinue [ACE-I/ARB] in people with GFR <30 ml/min/1.73m^2 as they remain nephroprotective".[11] Existing literature evaluating the risk-benefit of using ACE-I/ARB in individuals with advanced CKD is conflicting.[12–15] The ongoing STOP-ACEi trial aims to evaluate the difference in 3-year eGFR, randomizing 410 ACE-I/ARB users with advanced CKD to either continue or discontinue ACE-I/ARB.[16] However, the benefits of ACE-I/ARB therapy may also extend to cardiovascular disease and mortality.

Using data from a large, integrated health system, we assessed the association of ACE-I/ARB discontinuation with the risk of all-cause mortality, major adverse cardiovascular events (MACE), and end-stage kidney disease (ESKD) among ACE-I/ARB users whose eGFR dropped to below 30 ml/min/1.73m^2. As a secondary objective, we evaluated the effect of ACE-I/ARB discontinuation among users who experienced a decline in eGFR by ≥40% within one year, a surrogate end point for kidney failure used by the US Food and Drug Administration.[17]

Methods

Study setting and study population

We identified users of ACE-I/ARB from the Geisinger Health System, a fully integrated health care system that serves 45 counties in central and northeastern Pennsylvania. The local population has an estimated 1% annual outmigration rate.[18] The electronic health records provide patient-level data on outpatient prescriptions, problem lists, laboratory test results, inpatient and outpatient encounters, and demographic characteristics.

We first identified 162654 individuals who initiated ACE-I/ARB between year 2004 and 2018. Next, we subset the population to the 10810 individuals whose outpatient eGFR declined to below 30 ml/min/1.73m^2 after therapy initiation. Individuals who discontinued ACE-I/ARB before the initial drop to below 30 ml/min/1.73m^2 were excluded (N=5402). A window of 6 months after the eGFR decline was constructed to assess ACE-I/ARB discontinuation; thus, in primary analysis, baseline date of follow-up, T_0, was 6 months after the day of eGFR decline to a value <30 ml/min/1.73m^2. Individuals who discontinued and restarted ACE-I/ARB therapy within the 6-month period before T_0 (N=233) and those who did not meet our formal criteria for discontinuation but were off ACE-I/ARB at T_0 (N=317) were excluded. Further exclusion criteria included T_0 after the end of follow-up (N=214); the absence of serum potassium and systolic blood pressure measures in the year prior to the eGFR decline (N=303); <18 years of age at the time of the eGFR decline (N=3); and death before T_0 (N=324) or prevalent ESKD at T_0 (N=105) (**Figure 4-S 1**).

Treatment strategies under comparison

We compared individuals who stopped ACE-I/ARB within 6 months after a decline in eGFR to below 30 ml/min/1.73m^2 with those who did not. We defined discontinuation as

a gap in therapy longer than 60 days occurring before T_0. We allowed for switching between ACE-I and ARB, or to different medications within each class, given evidence suggesting ACE-Is and ARBs share similar mechanisms, benefits, and risks.[4,5,11]

Endpoints and follow-up

The primary endpoint was mortality over the subsequent five years after T_0. Secondary endpoints included MACE and ESKD. For all endpoints, follow-up was available up until January 25, 2019. MACE, defined as the first occurrence of death, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass after T_0, was ascertained using previously validated International Classification of Disease (ICD) procedure and diagnosis codes.[19] ESKD was captured by linking to the United States Renal Data System, which was available up until July 31, 2018. For the remaining six months between this date and January 25, 2019, the ICD procedure and diagnosis codes of kidney transplant and dialysis were used to ascertain ESKD cases (**Table 4-S 1**).

We investigated as additional outcomes hyperkalemia and AKI during follow-up. Hyperkalemia was defined as the first serum potassium level greater than 5.5 mEq/L occurring as an outpatient or as the first measure of an inpatient episode. AKI was obtained using the ICD diagnosis codes (**Table 4-S 2**).

Baseline Covariates

We defined baseline serum potassium level, systolic blood pressure, and serum creatinine as the most recent outpatient measure available within one year before the eGFR decline to below 30 ml/min/1.73m^2. We used the CKD-EPI equation to estimate GFR based on outpatient serum creatinine level.[20] Baseline comorbidities such as history of stroke,

congestive heart failure, diabetes, and coronary artery disease were defined based on the presence of the corresponding ICD codes. We also ascertained concurrent use of other medications such as statin, antiplatelet agents, and beta-blockers at the time of the eGFR decline, and whether a patient was hospitalized, had a nephrology visit, and the number of outpatient encounters during the one-year period prior to the eGFR decline. Other covariates included sex, race, age, and calendar year (categorized as 2004-2008, 2009-2013, 2014-2019) at the time of the eGFR decline.

Propensity-score matching

We performed nearest-neighbor propensity-score matching without replacement to 1:1 match individuals who discontinued ACE-I/ARB to those without discontinuation, using a caliper of 0.25 standard deviation of the propensity-score.[21] Covariates in the propensity-score model included baseline variables defined above. We chose these variables *a priori* to minimize indication bias that might confound the association between ACE-I/ARB discontinuation and the outcome. Balance between the two comparison groups was evaluated using the standardized mean difference across covariates, with an absolute standardized mean difference below 0.1 indicating successful balance.[22]

Statistical analysis

We described baseline characteristics of the study population by treatment group both before and after propensity-score matching using proportions for categorical variables and means and standard deviations for continuous variables. We used Kaplan Meier curves to depict survival over five years after T_0, stratified by treatment strategy. We then

assessed the association of ACE-I/ARB discontinuation with mortality using multivariable Cox proportional hazards regression analysis in the propensity-score matched sample, adjusting for all baseline covariates. We used linear spline forms of serum potassium with knots at 4 and 5 mEq/L, systolic blood pressure with knots at 90 and 140 mmHg, and age with knots at 45 and 65 years, to allow for non-linear relationship. We applied similar methods to assess the associations of ACE-I/ARB discontinuation with MACE, ESKD, hyperkalemia, and AKI. In cumulative incidence curves for ESKD, we illustrated the proportion remaining free of ESKD accounting for the competing risk of death.

We assessed whether the effect of ACE-I/ARB discontinuation differed by baseline diabetes, congestive heart failure, coronary artery disease, and history of stroke. We tested for potential effect modification by the presence of macroalbuminuria at baseline. Macroalbuminuria was defined as the latest measure within the three-year window before eGFR declined to below 30 ml/min/1.73m^2 and urine albumin to creatinine ratio>300 mg/g; if not available, urine protein to creatinine ratio>700 mg/g or dipstick measure of "++" or greater were also accepted.

To evaluate the association of ACE-I/ARB discontinuation following a ≥40% decline in eGFR within one year with the risks of mortality, MACE, and ESKD, we identified individuals who had a ≥40% decline in eGFR during treatment compared with the previous measure within a year. We repeated the primary analyses within this sample, with T_0 defined as 6 months after the first time eGFR decreased by ≥40% during ACE-I/ARB treatment.

Negative control

To illustrate the observed associations between ACE-I/ARB discontinuation and the endpoints of interest were not due to different health status between the two treatment groups, we compared the risk of bleeding, an outcome believed to be not affected by ACE-I/ARB use, between the propensity-score matched treatment groups, adjusting for antiplatelet agent use at the time of the eGFR decline. Bleeding was ascertained from emergency department visits and hospitalization episodes using ICD diagnosis codes.

Sensitivity analysis

Several sensitivity analyses were performed. First, we estimated the association between ACE-I/ARB discontinuation and ESKD using the Fine-Gray competing risk regression models to account for the competing risk of death.[23] Second, we used a target trial emulation technique allowing for the inclusion of the individuals who died or developed ESKD during the six months after the eGFR decline to below 30 ml/min/1.73m^2 with time-updated weighting (**eMethods** in the supplement).[24,25] Third, we excluded individuals with systolic blood pressure lower than 90 mmHg or serum potassium higher than 5.5 mEq/L at the time of the eGFR decline to below 30 ml/min/1.73m^2. Fourth, we restricted the study population to individuals who had been on ACE-I/ARB for at least six months at the time of the eGFR decline. Fifth, we excluded individuals with AKI at the time of eGFR decline, defined as an increase in serum creatinine by >100% compared with the previous outpatient measure within 1 year. Sixth, we excluded patients with a history of cancer determined by ICD diagnosis codes. Seventh, we evaluated whether discontinuation after eGFR decline to 20 ml/min/1.73m^2 had similar associations with the endpoints of interest. Finally, we used Rosenbaum's approach to explore the sensitivity

of our findings to unmeasured confounding.[26,27] All 95% confidence intervals (CIs) in the primary and sensitivity analyses were reported based on robust standard errors.

Results

Study population

There were 3909 individuals from the Geisinger Health System who met the inclusion criteria, with a mean age of 73.7 years (standard deviation 12.6 years); 62% were women. There were 1235 individuals who discontinued ACE-I/ARB within the 6 months after eGFR fell below 30 ml/min/1.73m^2 and 2674 individuals without such discontinuation. Compared to their counterparts, individuals who discontinued ACE-I/ARB were more often male, had slightly lower eGFR, higher serum potassium level, higher prevalence of congestive heart failure, and more likely to be on antiplatelet agents at the time of the eGFR decline (**Table 4-1**). On the other hand, they were less likely to have diabetes and less likely to be on statin and beta-blockers. Nearly all (N=1205, 98%) individuals in the discontinuation group were successfully matched to controls, resulting in a total of 2410 individuals in the propensity-score matched sample. The two treatment groups were closely balanced on all baseline covariates after propensity-score matching, with the absolute standardized mean difference below 0.1 for all covariates.

ACE-I/ARB discontinuation and mortality, MACE, and ESKD

Over a median follow-up of 2.9 years, 434 (35.1%) of the 1235 individuals who discontinued ACE-I/ARB within six months after eGFR declined to below 30 ml/min/1.73m^2 and 786 (29.4%) of the 2674 individuals without discontinuation died within five years after T_0 (**Figure 4-1 a, b**). Of note, 347 (28%) of the 1235 patients who

discontinued ACE-I/ARB within six months of the eGFR decline restarted therapy during the follow-up period. The association between ACE-I/ARB discontinuation and higher risk of mortality remained after adjusting for baseline covariates in the propensity-score matched sample (hazard ratio (HR): 1.39 [95% CI: 1.20-1.60]; **Table 4-2**).

Over a median follow-up of 2.7 years, there was a higher risk of MACE during the five-year period among those with ACE-I/ARB discontinuation (n=494, 40.0%) compared with those who did not discontinue (n=910, 34.0%; **Figure 4-2 a, b**). The association between ACE-I/ARB discontinuation and MACE remained in the propensity-score matched sample (HR: 1.37 [95% CI: 1.20-1.56]).

Over a median follow-up of 2.7 years, a slightly higher proportion of individuals developed ESKD within five years among those who discontinued ACE-I/ARB within six months after eGFR dropped below 30 ml/min/1.73m^2 (N=87, 7.0%) compared with those who did not discontinue (N=176, 6.6%; **Figure 4-3 a, b**). In adjusted analysis within the propensity-score matched sample, ACE-I/ARB discontinuation was not significantly associated with risk of ESKD (HR: 1.19 [95% CI: 0.86-1.65]).

There was no effect modification of the associations of ACE-I/ARB discontinuation with mortality and MACE by baseline history of stroke, diabetes, congestive heart failure, or coronary artery disease. However, the presence of baseline diabetes modified the association between ACE-I/ARB discontinuation and ESKD (p=0.013). Of the 915 and 1982 individuals from the discontinuation and non-discontinuation group, respectively, who had a baseline measure of urine albumin to creatinine ratio, urine protein to creatinine ratio, or dipstick, 1794 were included in the

propensity-score matched sample. There was no significant effect modification of the association of ACE-I/ARB discontinuation with mortality, MACE, and ESKD by the presence of macroalbuminuria.

Additional outcomes

Over a median follow-up of 2.3 years, individuals who discontinued ACE-I/ARB within six months after eGFR fell below 30 ml/min/1.73m^2 had a lower risk of hyperkalemia (N=193, 15.6%) compared with those who did not discontinue (N=593, 22.2%; **Figure 4-S 2**). In the propensity-score matched sample, the association remained significant (HR: 0.65 [95% CI: 0.54-0.79]).

Although the risk of AKI was slightly lower among individuals with ACE-I/ARB discontinuation (N=343, 27.8%) than those without (N=806, 30.1%) in the overall sample, the difference was not significant after accounting for baseline covariates in the propensity-score matched sample (HR: 0.92 [95% CI: 0.79-1.07]).

ACE-I/ARB discontinuation after eGFR decline by ≥40%

Among the 4251 individuals with an eGFR decline by ≥40% over one year while on ACE-I/ARB, 1189 discontinued ACE-I/ARB within six months of the eGFR decline and the remaining 3062 did not (**Table 4-S 3**). Over a median follow-up of 3.3 years, a higher proportion of individuals who discontinued ACE-I/ARB died (N=388; 32.6%) compared with those without discontinuation (N=627; 20.5%). A similar trend held for 5-year MACE, with 448 (37.7%) and 777 (25.4%) individuals experiencing MACE among those with and without ACE-I/ARB discontinuation, respectively. The proportion of individuals developing ESKD was also slightly higher among those with ACE-I/ARB

discontinuation (48; 4.0%), compared with those without discontinuation (63; 2.1%) (**Figure 4-1 - Figure 4-3 c, d**). In adjusted analyses within the propensity-score matched sample, ACE-I/ARB discontinuation was associated with a higher risk of mortality (HR: 1.53 [95% CI: 1.31-1.79]), MACE (HR: 1.40 [95% CI: 1.22-1.62]), but not ESKD (HR: 1.50 [95% CI: 0.91-2.47]).

Negative control

Individuals who discontinued ACE-I/ARB within six months after eGFR fell below 30 ml/min/1.73m^2 showed similar risks of bleeding compared with their propensity-score matched peers without discontinuation (**Figure 4-S 3;** HR: 0.88 [95% CI: 0.66-1.16]).

Sensitivity analysis

All sensitivity analyses yielded similar associations of ACE-I/ARB discontinuation with mortality, MACE, and ESKD (**Results** in the supplement). Our results were moderately sensitive to an unobserved confounder. To attribute the observed associations to an unobserved covariate that increased the odds of mortality and MACE by 50%, the covariate would need to more than double the odds of ACE-I/ARB discontinuation.

Discussion

In this large, real-world study of individuals who experienced eGFR decline while on ACE-I or ARB therapy, discontinuation of therapy after eGFR decline was associated with a higher risk of death and MACE, but no statistically significant difference in the risk of ESKD. The findings were robust to a number of sensitivity analyses including using a target trial emulation technique, and excluding individuals with hypotension, hyperkalemia, AKI, or a history of cancer at the time of the eGFR decline. ACE-I/ARB

discontinuation was associated with a lower risk of hyperkalemia, consistent with existing evidence;[7] however, this risk did not appear to outweigh the potential cardiovascular and survival benefits of continuing ACE-I/ARB therapy.

Although our study is one of the first to evaluate the long-term risks of ACE-I/ARB discontinuation among individuals who experience CKD progression, others have evaluated the association of ACE-I/ARB use with long-term outcomes or discontinuation with short-term changes in eGFR. A meta-analysis of clinical trials showed that ACE-I/ARB use reduced risk of kidney failure and cardiovascular events in patents with CKD.[28] Similarly, an observational cohort study of US veterans with CKD found survival benefits associated with the administration of ACE-I/ARB across all eGFR levels, including eGFR <30 ml/min/1.73m^2.[29] A trial randomizing 224 patients with serum creatinine levels of 3.1 to 5.0 mg/dL to benazepril or placebo showed a 43% lower risk of the composite of doubling of serum creatinine, ESKD, or death associated with benazepril.[13] *Post hoc*, secondary analyses of the RENAAL trial and the REIN trial both suggested benefits of ACE-I/ARB in individuals with low GFR.[14,15] However, an observational study of 52 individuals with stage G4 or 5 CKD reported an eGFR increase after ACE-I/ARB discontinuation, and the authors concluded "discontinuation of ACEi/ARB has undoubtedly delayed the onset of RRT [renal replacement therapy] in the majority of those studied".[12] An ongoing clinical trial aims to detect the difference in 3-year GFR among individuals with stage G4-5 CKD.[16] Our results add a longer observation period, a larger sample size of individuals with eGFR below 30 ml/min/1.73m^2, and ascertainment of hard outcomes with less concern for acute effects in GFR due to therapy.

Our study had several limitations. First, ACE-I/ARB use was obtained through prescription records and we could not verify actual medication dispensation or intake. Second, our study was observational and susceptible to unmeasured confounding. However, the two comparison groups were matched closely not only on measured clinical and demographic factors but also on variables including the number of outpatient visits, hospitalization status, and the presence of a nephrology visit during the year before eGFR decline. Third, we performed an intention-to-treat analysis providing an effect estimate based on the initial treatment decision; however, many patients who discontinued therapy then restarted ACE-I/ARB within the follow-up period. Thus, our effect estimate was likely conservative due to dilution caused by non-adherence to discontinuation status during follow-up.[30] Fourth, we treated ACE-I/ARB discontinuation as binary without dose-response assessment. Fifth, ESKD is itself a treatment decision and likely varies by provider. Finally, the majority of our study population was white.

Our study also had strengths. First, we used a "doubly robust" method to minimize confounding by indication through propensity-score matching and further adjustment for baseline demographic and clinical variables. Second, we conducted a number of sensitivity analyses with robust findings. Third, our study sample contained approximately 4000 individuals in routine clinical practice, which is a considerable sample size of ACE-I/ARB users with an eGFR decline to below 30 ml/min/1.73m^2. Fourth, we assessed a negative control and observed similar risks of bleeding between the two treatment groups. This result helped mitigate concerns that the observed higher risks of death and MACE associated with ACE-I/ARB discontinuation might reflect poorer health status among those who discontinued ACE-I/ARB. Finally, we also studied

individuals who experienced ≥40% decline in eGFR within one year to address potential misclassification of advanced CKD and to provide additional insights for clinical practice.

Conclusion

We found a higher risk of mortality and MACE associated with ACE-I/ARB discontinuation after eGFR decline to below 30 ml/min/1.73m^2, but no significant difference in the risk of ESKD. Similar patterns held for individuals with a ≥40% decline in eGFR. Our findings suggest that continuing ACE-I/ARB in patients with declining renal function may provide cardiovascular and survival benefits without excess risks of ESKD.

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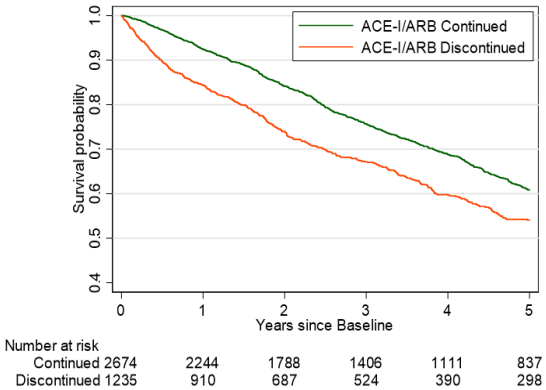
Figure 4- 1. Cumulative incidence of all-cause mortality, by ACE-I/ARB discontinuation status

a)



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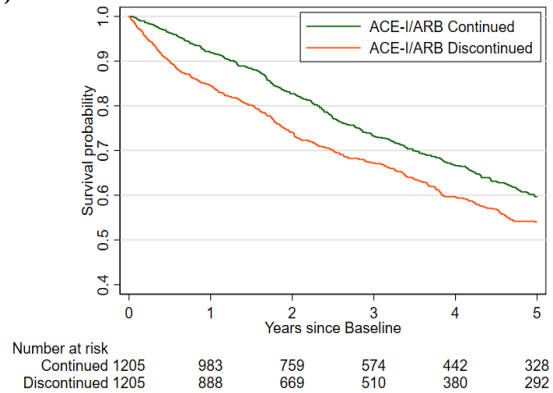

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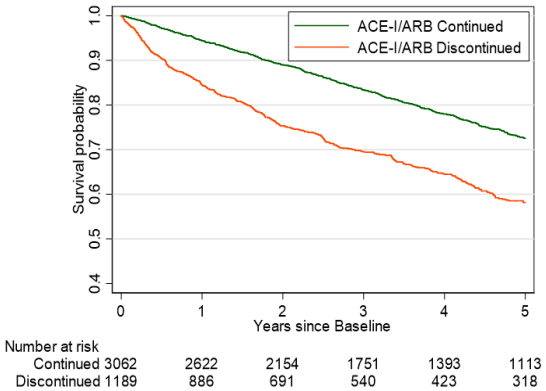

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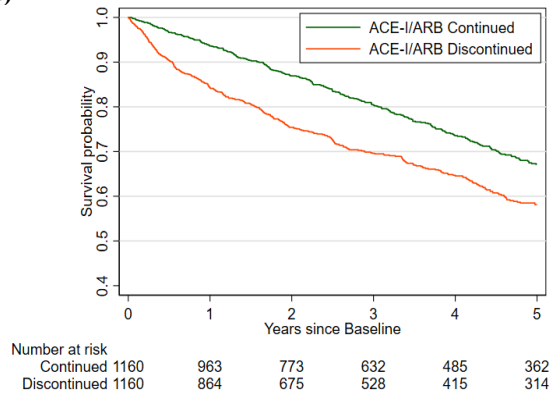
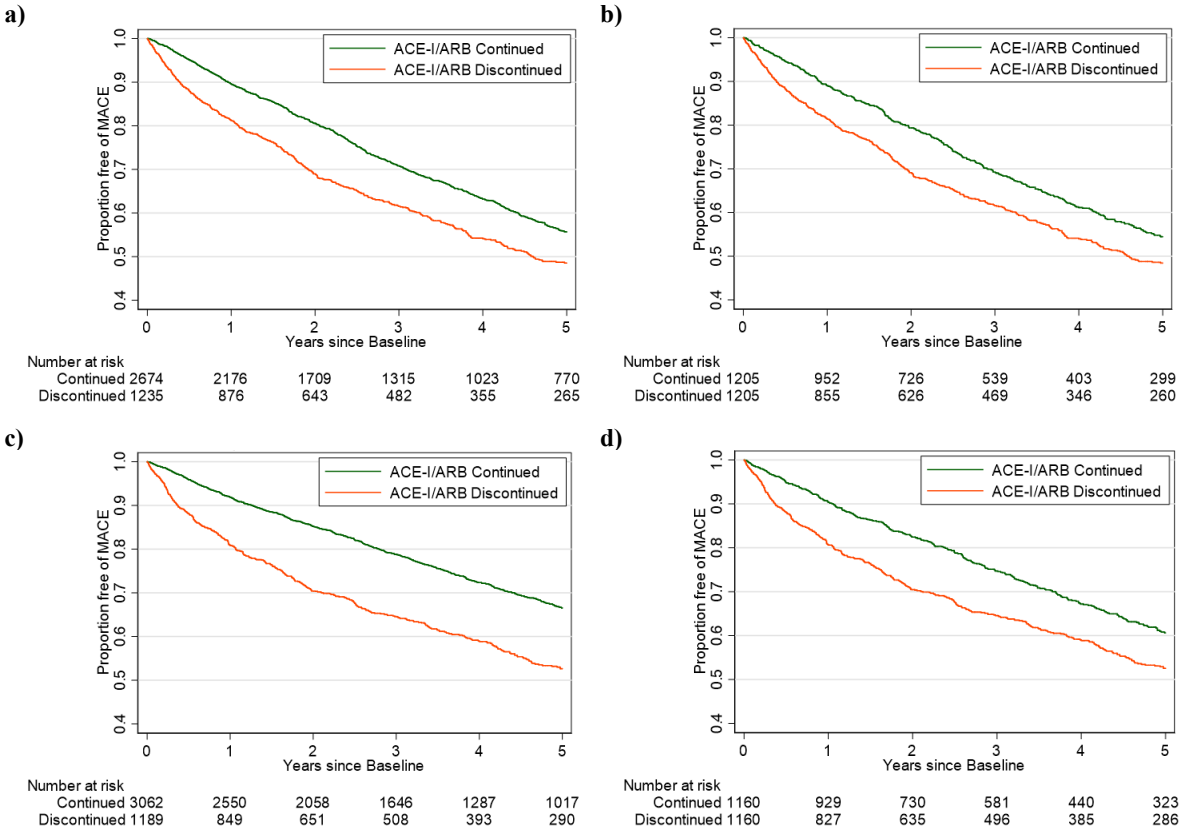


Note:

a) Among patients with an eGFR decline to below 30 ml/min/1.73m^2, full sample
b) Among patients with an eGFR decline to below 30 ml/min/1.73m^2, propensity-score matched sample
c) Among patients with a ≥ 40% decline in eGFR within one year, full sample
d) Among patients with a ≥ 40% decline in eGFR within one year, propensity-score matched sample

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate.

Figure 4- 2. Cumulative incidence of MACE, by ACE-I/ARB discontinuation status

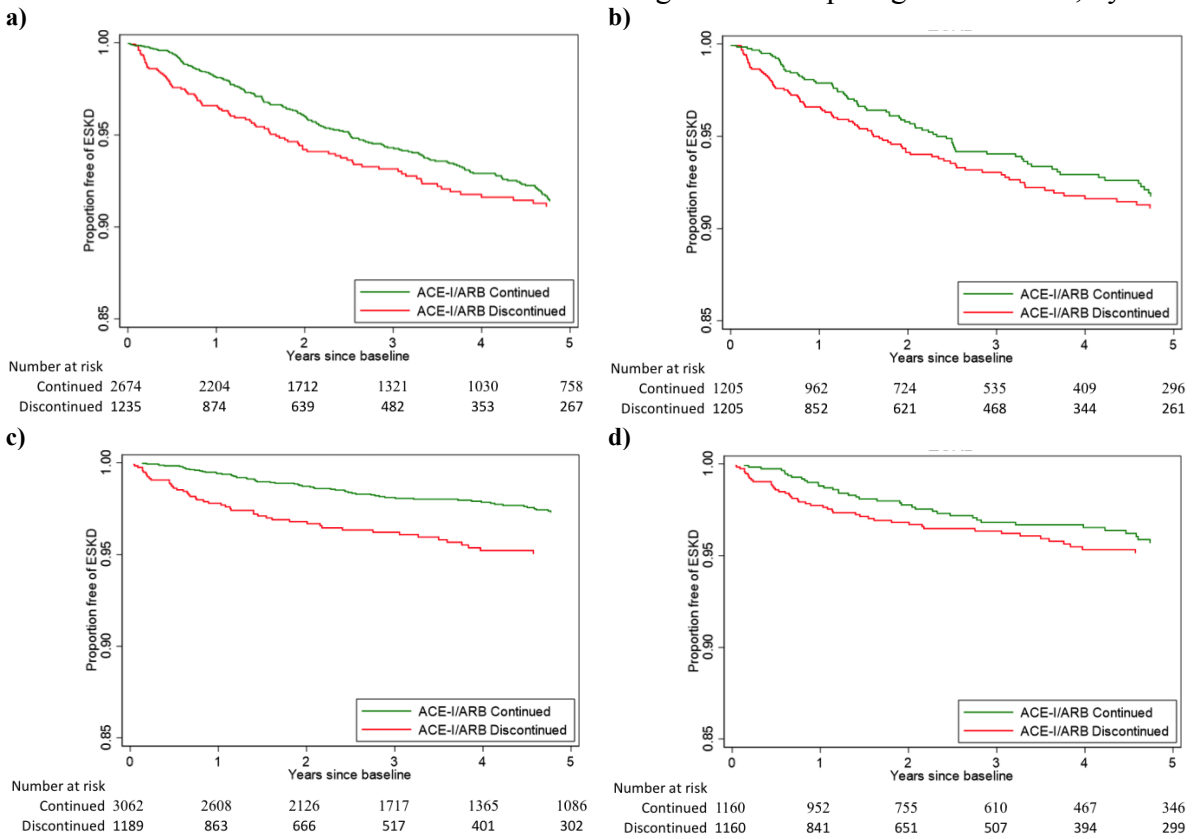


Note:

a) Among patients with an eGFR decline to below 30 ml/min/1.73m^2, full sample
b) Among patients with an eGFR decline to below 30 ml/min/1.73m^2, propensity-score matched sample
c) Among patients with a ≥ 40% decline in eGFR within one year, full sample
d) Among patients with a ≥ 40% decline in eGFR within one year, propensity-score matched sample

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; MACE, major adverse cardiovascular events; eGFR, estimated glomerular filtration rate.

Figure 4- 3. Cumulative incidence of ESKD accounting for the competing risk of death, by ACE-I/ARB discontinuation status



Note:

a) Among patients with an eGFR decline to below 30 ml/min/1.73m^2, full sample
b) Among patients with an eGFR decline to below 30 ml/min/1.73m^2, propensity-score matched sample
c) Among patients with a ≥ 40% decline in eGFR within one year, full sample
d) Among patients with a ≥ 40% decline in eGFR within one year, propensity-score matched sample

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate.

Table 4- 1. Baseline characteristics by ACE-I/ARB discontinuation status, before and after propensity-score matching

Baseline Characteristics	Pre-matching (N=3909)			Post-matching (N=2410)		
	Discontinued (N=1235)	Control (N=2674)	Standardized mean difference	Discontinued (N=1205)	Control (N=1205)	Standardized mean difference
Age, mean (SD), years	73.0 (12.9)	74.0 (12.4)	0.083	73.1 (12.8)	73.3 (13.2)	0.011
eGFR[a], mean (SD), ml/min/1.73m^2	23.2 (5.7)	25.5 (4.2)	0.462	23.6 (5.3)	23.9 (5.3)	0.073
Potassium[a], mean (SD), mEq/L	4.8 (0.8)	4.6 (0.6)	0.266	4.8 (0.7)	4.8 (0.7)	0.036
Systolic blood pressure[a], mean (SD), mmHg	125.0 (22.5)	127.1 (20.2)	0.095	125.3 (22.3)	125.4 (20.1)	0.004
Number of outpatient visits[b], mean (SD)	6.7 (5.5)	5.9 (4.5)	0.158	6.6 (5.4)	6.4 (5.0)	0.032
Female, N (%)	711 (57.6)	1695 (63.4)	0.119	696 (57.8)	706 (58.6)	0.017
Black race, N (%)	22 (1.8)	52 (1.9)	0.012	22 (1.8)	25 (2.1)	0.018
Coronary artery disease[c], N (%)	547 (44.3)	1180 (44.1)	0.003	533 (44.2)	528 (43.8)	0.008
Congestive heart failure[c], N (%)	404 (32.7)	807 (30.2)	0.055	395 (32.8)	398 (33.0)	0.005
Diabetes[c], N (%)	582 (47.1)	1332 (49.8)	0.054	572 (47.5)	589 (48.9)	0.028
History of stroke[c], N (%)	239 (19.4)	560 (20.9)	0.040	236 (19.6)	245 (20.3)	0.019
Statin use, N (%)	694 (56.2)	1721 (64.4)	0.167	681 (56.5)	692 (57.4)	0.018
Beta-blocker use, N (%)	709 (57.4)	1682 (62.9)	0.112	689 (57.2)	676 (56.1)	0.022
Antiplatelet agent use, N (%)	524 (42.4)	1113 (41.6)	0.016	505 (41.9)	501 (41.6)	0.007
Hospitalization[b], N (%)	20 (1.6)	44 (1.7)	0.002	20 (1.7)	19 (1.6)	0.007
Nephrology visit[b], N (%)	206 (16.7)	512 (19.2)	0.064	204 (16.9)	188 (15.6)	0.036
Calendar year, N (%)						
2004-2008	175 (14.2)	463 (17.3)	0.086	173 (14.4)	176 (14.6)	0.007
2009-2013	449 (36.4)	1022 (38.2)	0.039	437 (36.3)	429 (35.6)	0.014
2014-2019	611 (49.5)	1189 (44.5)	0.100	595 (49.4)	600 (49.8)	0.008

[a] Most recent measure within the year before eGFR declined to below 30 ml/min/1.73m^2; [b] Assessed during the one-year window before baseline; [c] Any time before baseline. **Abbreviations**: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate

Table 4- 2. Association of ACE-I/ARB discontinuation with overall mortality, MACE, and ESKD

Hazard ratio (95% confidence interval)[a]	Overall mortality	MACE	ESKD
ACE-I/ARB discontinuation after an eGFR decline to <30 ml/min/1.73m^2	1.39 (1.20-1.60)	1.37 (1.20-1.56)	1.19 (0.86-1.65)
ACE-I/ARB discontinuation after an eGFR decline by ≥ 40%	1.53 (1.31-1.79)	1.40 (1.22-1.62)	1.50 (0.91-2.47)

[a] Adjusted for baseline age, gender, race, serum potassium level, systolic blood pressure, eGFR, history of stroke, congestive heart failure, diabetes, coronary artery disease, concurrent use of statin, antiplatelet agents, and beta-blockers, calendar year at the time of the eGFR decline, whether a patient was hospitalized, had a nephrology visit, and the number of outpatient encounters during the one-year period prior to the eGFR decline in the propensity-score matched sample.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events; ESKD, end-stage kidney disease.

Supplement

Supplemental Methods. Target trial emulation

As a sensitivity analysis, we used a target trial emulation technique allowing for the inclusion of the patients who died or developed ESKD during the six months after the eGFR decline to below 30 ml/min/1.73m^2. In this method, T_0 was considered the day after eGFR declined below 30 ml/min/1.73m^2. All eligible patients were duplicated and assigned to either the strategy of ACE-I/ARB continuation or discontinuation within 6 months. At each 30-day increment after T_0, patients were assessed for compliance with the assigned treatment strategy. Those who deviated from the assigned treatment strategy were censored. For example, if a patient assigned to the continuation arm was not on ACE-I/ARB therapy at day 60, he would be censored at that time. To account for the selection bias potentially introduced by censoring, we applied time-varying weighting by the inverse probability of remaining on the assigned treatment strategy (i.e., remaining uncensored). Weights were determined using a pooled logistic regression model restricted to the first six months of follow-up with discontinuation as the outcome. The model included all baseline covariates, month and its quadratic term, and time varying covariates including eGFR, serum potassium level, systolic blood pressure, history of stroke, diabetes, congestive heart failure, coronary artery disease, hospitalization status, the number of outpatient encounters, and whether a patient had a nephrology visit during the one year prior to the beginning of each monthly interval, and concurrent use of statin, antiplatelet agents, and beta-blockers. Weights were truncated at the 99.5th percentile. Then, we estimated the association of ACE-I/ARB discontinuation with death, MACE, and ESKD using pooled logistic regression. Outcome models included an indicator

variable for the assigned treatment strategy, month of follow-up and its quadratic term, and all the baseline covariates. 95% CIs of the HRs were estimated using a nonparametric bootstrap with 500 samples.

Supplemental Results. Sensitivity analyses

Using the Fine-Gray method accounting for the competing risk of death, ACE-I/ARB discontinuation was not significantly associated with increased risk of ESKD (sHR: 1.11 [95% CI: 0.81-1.53]). Using the target trial emulation method in which patients were not required to survive free of ESKD for six months after eGFR dropped below 30 ml/min/1.73m^2, we detected similar associations of ACE-I/ARB discontinuation with mortality (HR: 1.59 [95% CI: 1.43-1.79]), MACE (HR: 1.51 [95% CI: 1.36-1.69]), and ESKD (HR: 1.26 [95% CI: 0.99-1.65]), adjusted for baseline covariates.

Excluding patients with hypotension or hyperkalemia at the time of the eGFR decline yielded a subsample of 1028 and 2447 patients in the discontinuation and non-discontinuation group, respectively. In the propensity-score matched cohort of 2052 patients, we found substantively similar associations of ACE-I/ARB discontinuation with mortality (HR: 1.38 [95% CI: 1.18-1.61]), MACE (HR: 1.32 [95% CI: 1.14-1.52]), and ESKD (HR: 1.36 [95% CI: 0.94-1.98]).

In another sensitivity analysis limited only to patients who had been on ACE-I/ARB for at least six months at the time of the eGFR decline to below 30 ml/min/1.73m^2, we identified 992 and 2281 patients from the discontinuation and non-discontinuation group, respectively. Based on the propensity-score matched sample of 1940 patients, we found similar patterns as ACE-I/ARB discontinuation appeared to be associated with

higher risks of mortality (HR: 1.30 [95% CI: 1.11-1.53]) and MACE (HR: 1.29 [95% CI: 1.11-1.51]), but not significantly different risk of ESKD (HR: 1.22 [95% CI: 0.82-1.80]).

Excluding people with apparent stage 2 acute kidney injury at the time of eGFR decline to below 30 ml/min/1.73m^2, we yielded 925 and 2343 patients from the discontinuation and non-discontinuation group, respectively. Based on the propensity-score matched sample of 1830 patients, we also found ACE-I/ARB discontinuation was associated with higher risks of mortality (HR: 1.34 [95% CI: 1.15-1.57]) and MACE (HR: 1.33 [95% CI: 1.15-1.55]), but not ESKD (HR: 1.04 [95% CI: 0.73-1.49]).

Excluding people with a history of cancer at the time of eGFR decline to below 30 ml/min/1.73m^2 yielded a sample of 930 and 2082 and individuals from the discontinuation and non-discontinuation group, respectively. Based on the propensity-score matched sample of 1802 patients, ACE-I/ARB discontinuation was associated with higher risks of mortality (HR: 1.49 [95% CI: 1.24-1.78]) and MACE (HR: 1.43 [95% CI: 1.21-1.69]) but not ESKD (HR: 1.40 [95% CI: 0.98-2.00]).

Among the 1217 individuals with an eGFR decline to below 20 ml/min/1.73m^2 while on ACE-I/ARB therapy, 572 discontinued ACE-I/ARB within six months of the eGFR decline and the remaining 645 did not. A total of 514 (90%) individuals in the discontinuation group were successfully matched to controls, resulting in a total of 1028 individuals in the propensity-score matched sample. Similarly, ACE-I/ARB discontinuation was associated with a higher risk of mortality (HR: 1.34 [95% CI: 1.10-1.64]), MACE (HR: 1.27 [95% CI: 1.05-1.53]), but not ESKD (HR: 1.27 [95% CI: 0.89-1.82]), adjusted for baseline covariates in the propensity-score matched sample.

Table 4-S 1. Diagnosis and procedure codes used to define end-stage kidney disease (ESKD)

Code system	Codes
Current Procedural Terminology (CPT)	90919-90999
Healthcare Common Procedure Coding System (HCPCS)	G0308-G0327, G0257, Q4081
International classification of disease, 9th edition, clinical modification (ICD-9-CM)	39.95, 54.98, 55.69, V56x, 585.5, 585.6, V42.0, 996.81
International classification of disease, 10th edition, clinical modification (ICD-10-CM)	5A1Dx, 3E1M39Z, 0TYx, Z49x, N18.5, N18.6, Z94.0, T86.1x

Note: The symbol "x" at the end of a code represents any characters. ESKD date was the earlier date of kidney transplant and dialysis. Kidney transplant date and dialysis date were both obtained from THE United States Renal Data System (USRDS), which covered through 7/31/2018. For the period after 7/31/2018, kidney transplant was coded as the date of ICD procedure codes of kidney transplant, or the first date of ICD diagnosis codes of kidney transplant in inpatient or problem list when there were at least another two ICD diagnosis codes of kidney transplant in other encounters within one year if procedure codes were not present. Similarly, for dialysis after 7/31/2018, it was defined as the date of ICD diagnosis code of stage V chronic kidney disease or ESKD when there was a CPT, HCPSC and ICD codes of dialysis within 7 days later, or the date of the first CPT, HCPSC and ICD codes of dialysis when there were at least three dialysis codes that covered longer than a month with intervals between any two consecutive codes within three months.

Table 4-S 2. International classification of disease, 9th and 10th editions, clinical modification (ICD-9-CM, ICD-10-CM) used to define disease conditions

Disease Conditions	ICD-9-CM codes	ICD-10-CM codes
Diabetes	250.x	E10.x, E11.x, E13.x
Congestive heart failure	428.x	I50.x
Coronary artery disease	410.x, 411.0, 411.8x, 412, 414.x, 36.1x	I21.x, I22.x, I23.x, I24.x, I25.x
Stroke	43x, V12.54	I6x
Cancer	14x-20x	Cx
Bleeding	531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 456.0, 456.20, 530.7, 530.82, 578x, 455.2, 455.5, 455.8, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 593.81, 599.7x, 626.8, 626.2, 626.6, 430, 431, 432x, 852.0x, 852.2x, 852.4x, 853.0x, 423.0, 459.0, 568.81, 719.1x, 784.7, 784.8, 786.3x	K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.01, K29.21, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K31.811, I85.01, I85.11, K22.6, K22.8, K92.0, K92.1, K92.2, K64.4, K64.8, K57.11, K57.13, K57.31, K57.33, K66.1, K62.5, K55.21, R31.9, R31.0, R31.29, N93.8, N92.0, N92.1, I60.9, I61.9, I62.1, I62.00, I62.9, S06.6X0A, S06.6X1A, S06.6X2A, S06.6X3A, S06.6X4A, S06.6X5A, S06.6X6A, S06.6X7A, S06.6X8A, S06.6X9A, S06.5X0A, S06.5X1A, S06.5X2A, S06.5X3A, S06.5X4A, S06.5X5A, S06.5X6A, S06.5X7A, S06.5X8A, S06.5X9A, S06.4X0A, S06.4X1A, S06.4X2A, S06.4X3A, S06.4X4A, S06.4X5A, S06.4X6A, S06.4X7A, S06.4X8A, S06.4X9A, S06.360A, S06.361A, S06.362A, S06.363A, S06.364A, S06.3605A, S06.366A, S06.367A, S06.368A, S06.369A, I31.2, R58, K66.1, M25.00, M25.019, M25.029, M25.039, M25.049, M25.059, M25.069, M25.073, M25.076, M25.08, R04.0, R04.1, R04.2, R04.9, R04.89
Acute kidney injury	584.x	N17.x

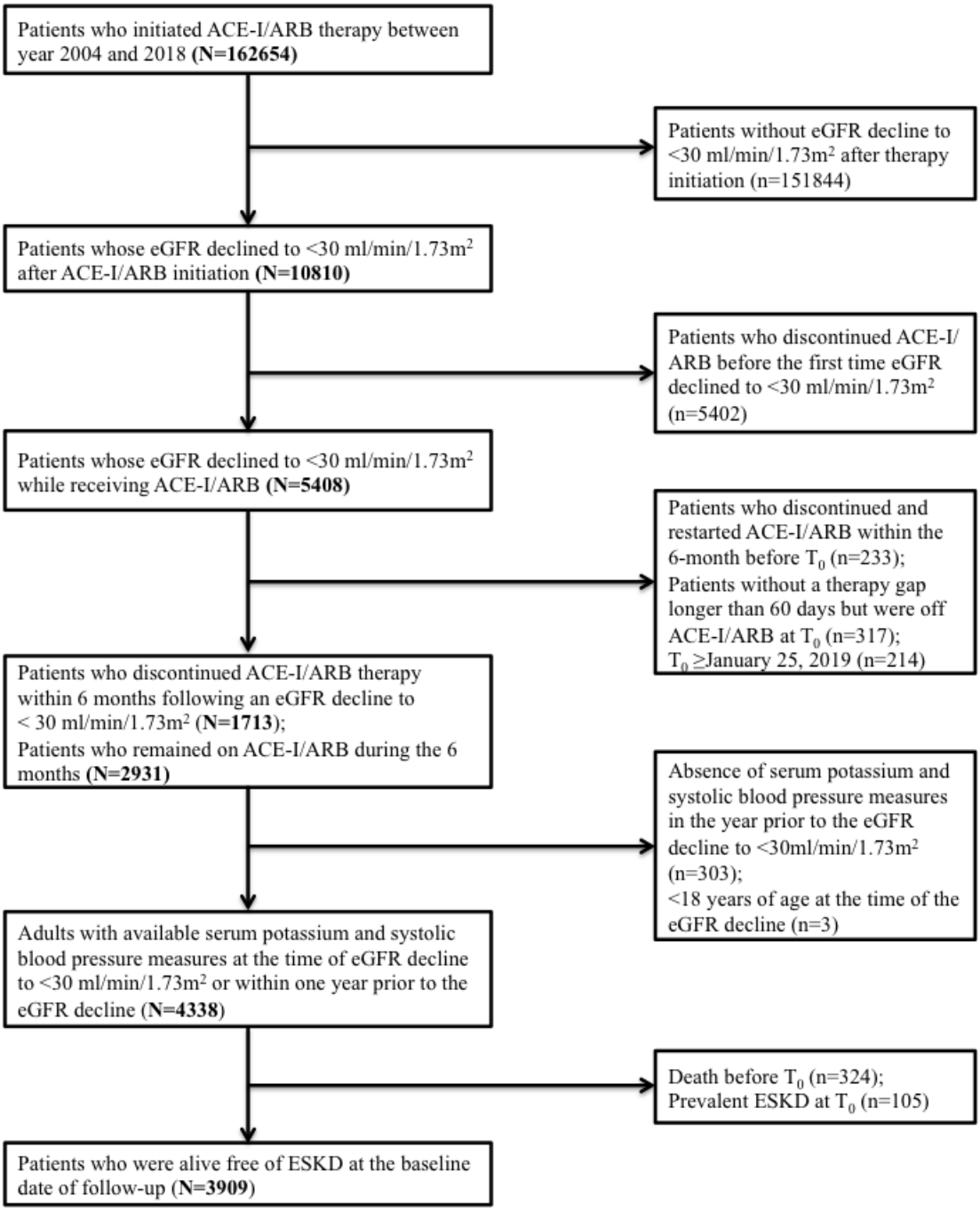
Note: The symbol "x" at the end of a code represents any characters.

Table 4-S 3. Baseline characteristics of patients with ≥40% eGFR decline

Baseline Characteristics	Pre-matching (N=4251)			Post-matching (N=2320)		
	Discontinued (N=1189)	Control (N=3062)	Standardized mean difference	Discontinued (N=1160)	Control (N=1160)	Standardized mean difference
Age, mean (SD), years	68.9 (13.2)	66.4 (13.2)	0.185	68.8 (13.1)	68.0 (13.1)	0.059
eGFR[a], mean (SD), ml/min/1.73m^2	29.4 (13.5)	37.7 (13.1)	0.626	29.8 (13.4)	30.5 (12.5)	0.059
Potassium[a], mean (SD), mEq/L	4.7 (0.8)	4.5 (0.6)	0.313	4.7 (0.8)	4.6 (0.7)	0.060
Systolic blood pressure[a], mean (SD), mmHg	122.3 (21.4)	124.9 (20.1)	0.123	122.5 (21.4)	122.8 (20.9)	0.014
Number of outpatient visits[b], mean (SD)	7.1 (5.7)	6.7 (4.9)	0.080	7.1 (5.7)	7.1 (5.2)	0.007
Female, N (%)	641 (53.9)	1809 (59.1)	0.104	632 (54.5)	658 (56.7)	0.045
Black race, N (%)	20 (1.7)	92 (3.0)	0.087	20 (1.7)	15 (1.3)	0.035
Coronary artery disease[c], N (%)	458 (38.5)	1091 (35.6)	0.060	445 (38.4)	440 (37.9)	0.009
Congestive heart failure[c], N (%)	331 (27.8)	667 (21.8)	0.141	319 (27.5)	333 (28.7)	0.027
Diabetes[c], N (%)	557 (46.9)	1501 (49.0)	0.044	545 (47.0)	537 (46.3)	0.014
History of stroke[c], N (%)	197 (16.6)	480 (15.7)	0.024	193 (16.6)	198 (17.1)	0.012
Statin use, N (%)	656 (55.2)	1877 (61.3)	0.124	644 (55.5)	638 (55.0)	0.010
Beta-blocker use, N (%)	642 (54.0)	1618 (52.8)	0.023	631 (54.4)	635 (54.7)	0.007
Antiplatelet agent use, N (%)	463 (38.9)	1134 (37.0)	0.039	450 (38.8)	441 (38.0)	0.016
Hospitalization[b], N (%)	19 (1.6)	69 (2.3)	0.048	19 (1.6)	23 (2.0)	0.026
Nephrology visit[b], N (%)	126 (10.6)	221 (7.2)	0.119	120 (10.3)	121 (10.4)	0.003
Calendar year, N (%)						
2004-2008	158 (13.3)	538 (17.6)	0.119	157 (13.5)	164 (14.1)	0.017
2009-2013	443 (37.3)	1120 (36.6)	0.014	432 (37.2)	446 (38.5)	0.025
2014-2019	588 (49.5)	1404 (45.9)	0.072	571 (49.2)	550 (47.4)	0.036

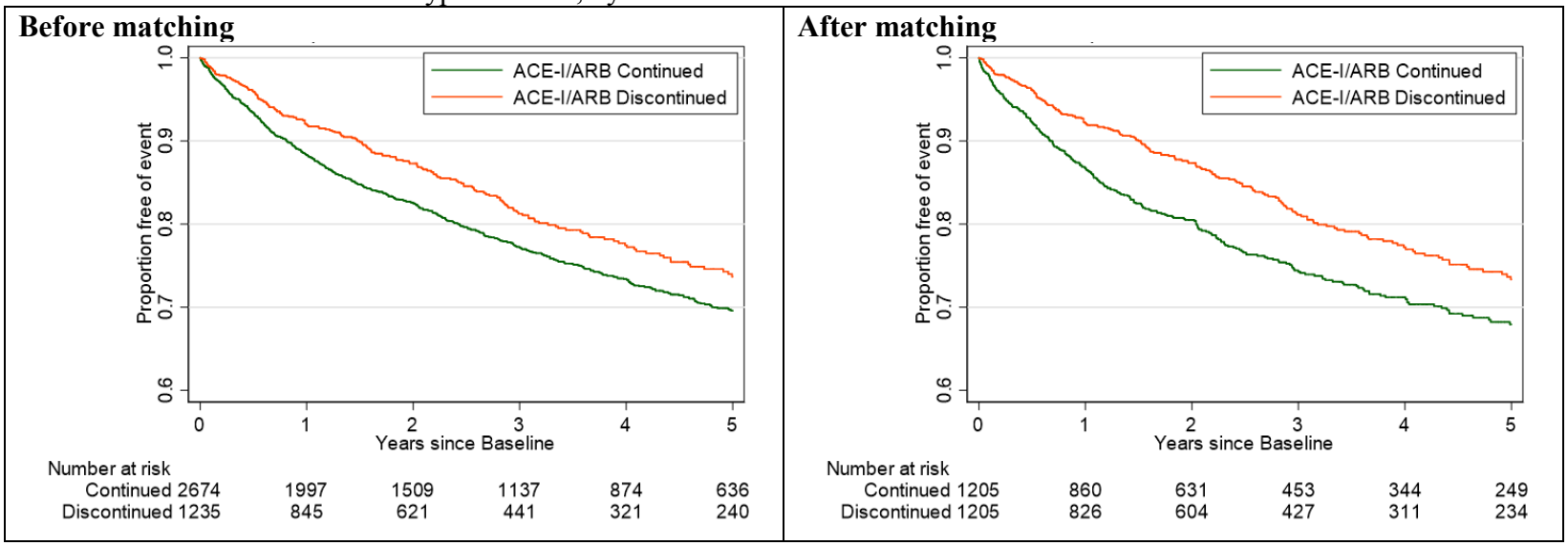
[a] Most recent measure within the year before eGFR declined to below 30 ml/min/1.73m^2; [b] Assessed during the one-year window before baseline; [c] Any time before baseline. Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate

Figure 4-S 1. Derivation of study population



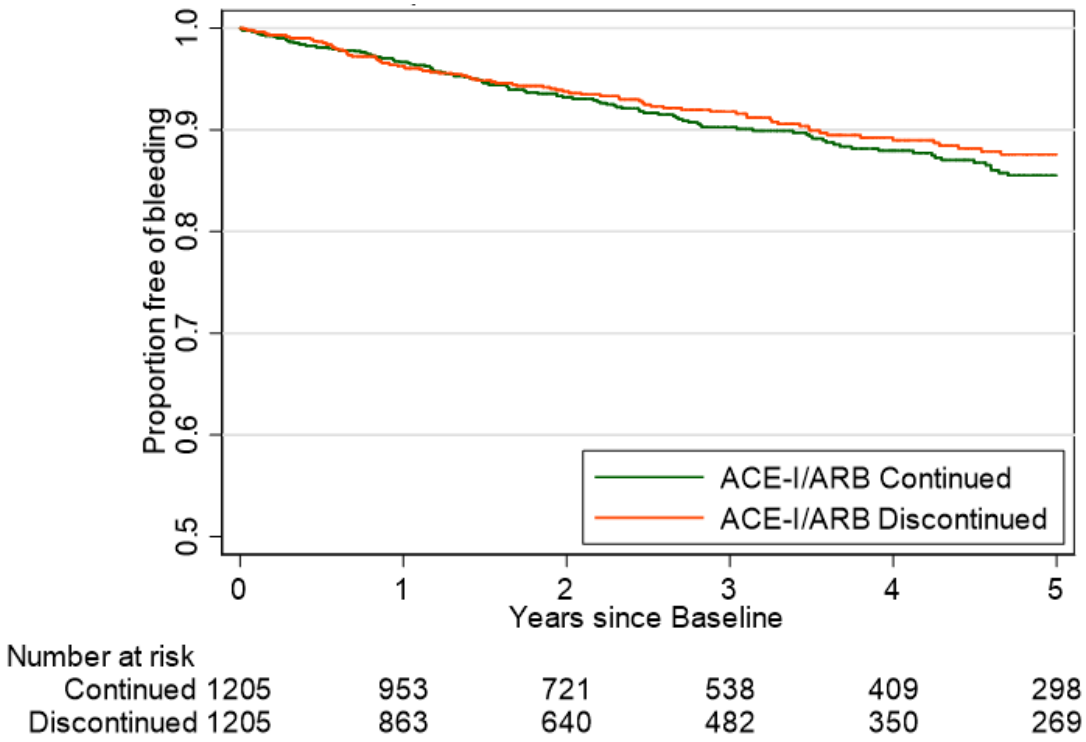
Abbreviations**:** ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate, ESKD, end-stage kidney disease

Figure 4-S 2. Cumulative incidence of hyperkalemia, by ACE-I/ARB discontinuation status



Abbreviations**:** ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

Figure 4-S 3. Cumulative incidence of bleeding, by ACE-I/ARB discontinuation status in the propensity-score matched sample



Abbreviations**:** ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

Chapter 5. Conclusion

Synthesis of evidence

Using electronic heath records data from the Geisinger Health System, this dissertation advanced the understanding of use of ACE-I/ARB in real-world clinical practice, and the risks and benefits associated with its use in individuals with low kidney function.

Our results showed underutilization of ACE-I/ARB among individuals without recorded contraindications or allergy to ACE-I/ARB as only 43.1% of those with ACR > 300 mg/g and only 40.9% of those with diabetes and ACR >30 mg/g initiated ACE-I/ARB within 6 months of the ACR measurement. We found that higher levels of albuminuria were associated with a greater chance of ACE-I/ARB initiation. Our results provide evidence that albuminuria test results change medical management, suggesting that adherence to albuminuria testing provides one opportunity to enhance utilization of ACE-I/ARB.

We also found that discontinuation of ACE-I/ARB was common in real-world clinical practice, especially for individuals with advanced CKD. We estimated that the majority of ACE-I/ARB users had a discontinuation in therapy by 5 years since initiation. There were strong associations of advanced CKD stages with therapy discontinuation, with patients with G4 disease (eGFR: 15-29 ml/min/1.73 m^2) more than twice as likely to discontinue therapy compared to people with eGFR ≥90 mL/min/1.73m^2. However, ACE-I/ARB discontinuation after eGFR decline to below 30 ml/min/1.73m^2 was found to be associated with a higher risk of mortality and MACE, and no significant difference in the risk of ESKD. Our findings suggest that continuing ACE-I/ARB in patients with declining renal function may provide cardiovascular and survival benefits without excess risks of ESKD.

Remaining questions and future directions

The study population was primarily white. However, previous studies have shown increased risk of angioedema associated with ACE-I/ARB among black individuals.[1] Thus, black individuals may be more likely to discontinue ACE-I/ARB therapy. Additionally, ACE-I/ARB is less effective in the black population.[2] Therefore, the risk-benefit balance of ACE-I/ARB among individuals with advanced CKD stage may vary by race. Future studies are needed to assess whether similar patterns hold in other racial and ethnicity groups.

Additionally, due to the observational nature of our study design, findings may be subject to unmeasured confounding. There is an ongoing clinical trial assessing the effect of stopping ACE-I/ARB among individuals with advanced CKD stages,[3] however, the study evaluates 3-year eGFR difference as the primary outcome without providing evidence on hard outcomes such as mortality. Additional trials are needed with longer follow up period to investigate the effect of ACE-I/ARB discontinuation on cardiovascular and survival outcomes.

Finally, the scope of this dissertation was evaluating the pattern and risk-benefit of ACE-I/ARB use without taking dosage into consideration. KDIGO also recommends "reduce dose by 50% in people with GFR <30 ml/min/1.73 m^2" with regards to ACE-I/ARB use in individuals with CKD.[4] To provide further evidence to maximize therapeutic potential of these medications, a next step would be to evaluate dosage of ACE-I/ARB in real-world clinical practice among individuals with advanced CKD.

Clinical and public health impact

Findings from this project have significant clinical and public health implications. We shed light on the real-world utilization pattern of ACE-I/ARB and the risk-benefit of discontinuing these medications in the setting of CKD. The findings have potentials of informing clinical guidelines

and real-world practice of prescribing ACE-Is and ARBs, which will affect numerous patients given how widely these agents are used.

By using real-world electronic health records data that cover a long period of time, this dissertation evaluated long-term impact of discontinuing ACE-I/ARB among individuals with advanced CKD. Additionally, our data captured a large number of real-world ACE-I/ARB users with advanced CKD, who tend to be under-represented in clinical trials. This study was one of the first to provide evidence for this patient group assisting their treatment decisions with regards to ACE-I/ARB discontinuation following CKD progression.

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2. Spence J. David, Rayner Brian L. Hypertension in Blacks. *Hypertension*. 2018;72(2):263-269. doi:10.1161/HYPERTENSIONAHA.118.11064

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Resume

EDUCATION

Johns Hopkins University, Baltimore, MD, USA Sept. 2017–Expected to graduate in May 2021
PhD in Epidemiology (Pharmacoepidemiology concentration). Cumulative GPA: 4.00/4.00.
Concurrent Master of Health Sciences (MHS) Program in Biostatistics. Cumulative GPA: 4.00/4.00.

University of Toronto, Toronto, ON, Canada Sept. 2013–June 2015
Master of Public Health (MPH) in Epidemiology. Cumulative GPA: 3.90/4.00.

University of Wisconsin-Madison, Madison, WI, USA Sept. 2011–May 2013
Master of Science in Industrial Engineering (Track: Health Systems Engineering). Cumulative GPA: 3.95/4.00.

Tsinghua University, Beijing, China Sept. 2007–July 2011
Bachelor of Science in Mechanical Engineering.

EXPERIENCE

Research Assistant, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD Sept. 2017–Present

- Doctoral thesis: investigated the effect of discontinuing angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) in patients with advanced chronic kidney disease; assessed the utilization pattern of these medications in the context of chronic kidney disease in real-world clinical practice.
  - Developed study proposal, constructed analytical cohorts from electronic health records, and performed statistical analyses.
  - First-authored three manuscripts published in peer-reviewed journals and presented findings at conferences.
- First-authored a study assessing how the cost of conducting clinical trials differs across various global regions.
- Teaching assistant for graduate courses: *Principles of Epidemiology* (2018-2019 and 2019-2020 academic years); *Introduction to Clinical Trials (2019-2020 academic year); Causal Inference in Medicine and Public Health I* (2019-2020 and 2020-2021 academic years).

Senior Analyst, Cancer Care Ontario, Toronto, ON Oct. 2015–Aug. 2017
Cancer Care Ontario is an agency of the provincial Government of Ontario responsible for improving cancer services.
Provided real-world evidence (RWE) support using multiple clinical and claims databases for the Ontario New Drug Funding Program and the Provincial Drug Reimbursement Programs

- Developed study protocols and conducted comparative effectiveness and health outcomes research to evaluate the safety and effectiveness of pharmaceutical products reimbursed in Ontario; set up study cohorts and performed statistical analysis; authored multiple internal reports, peer-reviewed manuscripts, and conference abstracts.
- Developed cancer care quality indicators; assessed the utilization and government expenditures on oral chemotherapy drugs covered by the Ontario Drug Benefit Program.

Research Officer (Apr.–Sept. 2015)**, Research Practicum** (Jan.–Mar. 2015), **University of Toronto,** Toronto, ON

- Conducted cost-effectiveness, comparative effectiveness, and health outcomes research based on multiple population-based datasets to evaluate treatment strategies for hepatocellular carcinoma, and health care utilization and costs attributable to the disease in Ontario; co-authored four research manuscripts.
- First-authored a systematic literature review and meta-analysis to assess the benefit, safety, and cost-effectiveness of screening in patients diagnosed with Barrett's esophagus.
- Managed project timelines and supervised research students; assisted in drafting ethics review protocols.

Epidemiology Practicum Student, St. Michael's Hospital, Toronto, ON Apr. 2014–Aug. 2014

- Assessed disparities in perinatal health outcomes between immigrant and native-born populations in Sweden using the Swedish Medical Birth Register; co-authored two manuscripts.

Research Assistant, University of Wisconsin-Madison, Madison, WI Sept. 2012–Aug. 2013

- Interviewed patients at five primary care clinics and performed statistical analysis to identify factors associated with patients' trust in electronic health records used in primary care; first-authored a manuscript.

PROFESSIONAL ACTIVITIES AND AWARD

- Conducted peer reviews for the following journals: *Informatics for Health and Social Care*, *Journal of the American Society of Nephrology*, *BMC Nephrology*, *American Journal of Epidemiology*
- 2019 American Society of Nephrology Kidney STARS award recipient

ANALYTICAL SOFTWARE

- SAS, R, STATA, TreeAge

PEER-REVIEWED MANUSCRIPT PUBLICATIONS

1. **Qiao Y**, Shin J, Chen TK, Inker LA, Coresh J, Alexander GC, Jackson JW, Chang AR, Grams ME. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among people with low estimated glomerular filtration rate. *JAMA Internal Medicine.* 2020 May 1;180(5):718-726.
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14. Urquia ML, **Qiao Y,** Ray JG, Liu C, Hjern A. Birth outcomes of foreign-born, native-born, and mixed couples in Sweden. *Paediatric and Perinatal Epidemiology*. 2015;29(2):123-130.
15. Juarez S, Urquia ML, Mussino E, Liu C, **Qiao Y,** Hjern A. Preterm disparities between foreign and Swedish born mothers depend on the method used to estimate gestational age. A Swedish population-based register study. *PLOS ONE*. [Accepted on February 2, 2021]
16. **Qiao Y,** Asan O, Montague E. Factors associated with patient trust in electronic health records used in primary care settings. *Health Policy and Technology*. 2015;4(4):357-363.

SELECTED CONFERENCE PRESENTATIONS

1. Poster presentation: "Globalization of clinical trials: variation in estimated regional costs of pivotal trials, 2015-2016". ISPE's 35th International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Philadelphia; August 2019.
2. Moderated poster presentation: "Discontinuation of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in chronic kidney disease". 2019 American Heart Association EPI Lifestyle Conference. Houston; March 2019.
3. Poster presentation: "The effectiveness and cost-effectiveness of implementing bicycle lanes in the prevention of obesity and permanent severe injury." 37th Annual Meeting of the Society for Medical Decision Making. St. Louis, Missouri; October 2015.
4. Poster presentation: "Screening and surveillance in patients with Barrett's esophagus for early detection of esophageal adenocarcinoma: a systematic review and meta-analysis." Ontario Institute for Cancer Research/ Cancer Care Ontario Health Services Research Program 7th Annual Meeting. Toronto, Ontario; June 2015.
5. Oral presentation: "Factors associated with patient trust in electronic health records used in a primary care setting: results from a survey." Fourth International Conference on Health, Wellness & Society. Vancouver, British Columbia; March 2014.